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Advances in the Management of Spinal Muscular Atrophy: Tailoring Treatment and Care Approaches to Improved Outcomes

Julie A. Parsons, MD

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For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

Spinal muscular atrophy (SMA) is a devastating neuromuscular disorder. Advances in understanding the pathology have led to gene therapy and other treatments which are altering the natural course of the disease. These new treatments are having a tremendous impact on patients and their families.

Key Points

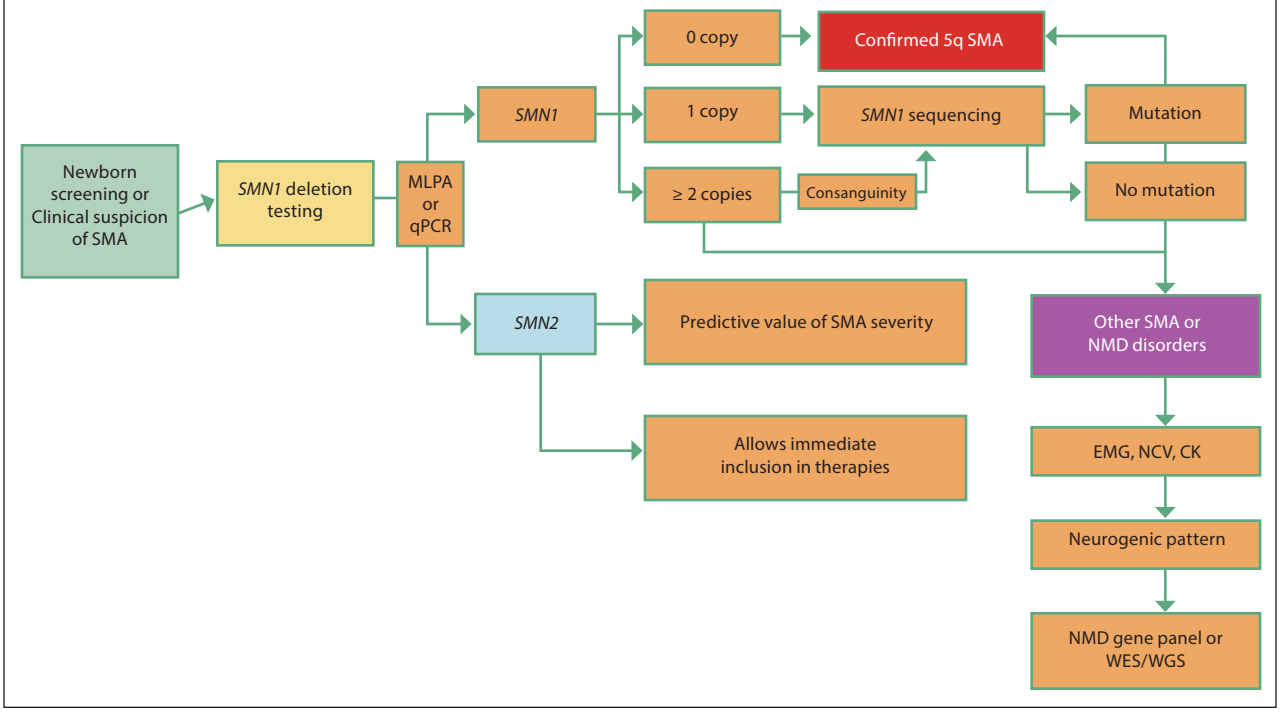
- Nusinersen, risdiplam, and onasemnogene abeparvovec-xioi are effective for SMA.
- Efficacy is improved when treatment is initiated as soon as possible after diagnosis.
- There are benefits to treatment later in life but the benefits are more modest.

SPINAL MUSCULAR ATROPHY (SMA) IS A clinically and genetically heterogeneous group of diseases with a loss of anterior horn cells, loss of lower motor neurons in the spinal cord and brainstem nuclei, and progressive muscle atrophy without involvement of the corticospinal tract. It is thought that 50 percent of motor neurons are already lost when an infant with Type 1 SMA is born. Poor weight gain, growth failure, restrictive lung disease, scoliosis, and joint contractures are common complications of untreated SMA. Death results primarily from respiratory failure.

The cause of the most common form of SMA is inactivating mutations of the survival of motor neuron 1 (SMN1) gene. The most common mutation is on the 5q chromosome and thus the disease is called 5q SMA or SMN1-related SMA.[1] This mutation accounts for 95 percent of SMA cases. SMN1-related SMA is an autosomal recessive neuromuscular disease caused by homozygous deletion or pathogenic variant of the SMN1 gene and for the rest of this article will be referred to as SMA. It has an incidence of 1:10,000 live births, occurs in all ethnicities, and has a carrier frequency of 1:40, similar to cystic fibrosis.

Someone with SMA has a non-functional SMN1 gene which normally produces 90 percent of the SMN protein.[2] They still have a functional SMN2 gene – a modifying gene – which produces smaller amounts of SMN protein. In humans, SMA disease severity correlates with the number of copies of the SMN2 gene and the level of functional protein produced. Those with one or two copies of the gene have SMA Type 1 disease, the most severe form.[3] Those with two to three copies have SMA Type 2 disease and four copies have SMA Type 3 disease. The correlation between number of copies and the phenotype of SMA is not perfect, for example someone can have two copies of SMN2 and have Type 3 SMA. People with five or more copies of

Exhibit 1: Diagnostic Algorithm[4]



CK = creatine kinase; EMG = electromyography; MLPA = multiplex ligation-probe amplification test; NCV = nerve conduction velocity; NMD = neuromuscular disease; qPCR = quantitative polymerase chain reaction; SMN1 = survival of motor neuron gene 1; SMN2 = survival of motor neuron gene 2; WES = whole-exome sequencing; WGS, whole-genome sequencing

SMN2 are clinically unaffected even though they have non-functioning SMN1. SMA is diagnosed based on genetic testing to identify non-functional SMN1 and the number of SMN2 gene copies (Exhibit 1).[4] Newborn screening for SMA was added to the federal Recommended Uniform Screening Panel in 2018. As of 2023, all states except Nevada have added SMA to their screening panels.[5]

Without newborn screening, it can be difficult to diagnose milder forms of SMA (Type 3 and 4), where less severe symptoms may overlap with other conditions and which have later in life onset of symptoms. Adolescents and adults may face a long diagnostic journey compared with children with more severe forms of SMA. In one survey, those with Type 3 disease had an 89.4-month diagnosis delay.[6] It is important to refer patients as quickly as possible for genetic testing where there is evidence of proximal weakness as this will reduce the time to diagnosis.

Those with SMA are also classified based on level of function as non-sitters, sitters, and walkers.[7] Non-sitters comprise approximately 60 percent of cases, sitters 30 percent, and walkers 10 percent. Without treatment only 8 percent of non-sitters survive to 20 months of age.[8,9] Without treatment, patients, especially those with more severe disease, require a significant amount of supportive care, physical therapy, nutrition care, and equipment including power chairs, walkers, noninvasive ventilation, and cough assist devices.

There are consensus guidelines on managing these patients and all patients with SMA are now recommended to receive treatment, even those with four copies of SMN2.[4,10,11] When the disease-modifying SMA treatments were first FDA approved, the guidelines did not recommend treatment in those with four copies but this changed because of evidence that disease expression does not always follow copy numbers. The guidelines cover diagnosis and genetic testing; nutrition, growth, and bone health; pulmonary, orthopedic, physical therapy and rehabilitation, and other organ system involvement care; acute care in the hospital setting, ethics and palliative care, and medication. Improved standards of care especially for nutrition and aggressive pulmonary care have dramatically improved the survival of those with SMA Type 1 even without specific treatments that alter the underlying pathology.[12,13] The prolongation of survival from improved care does not impact achievement of motor milestones – non-sitters will never become

Exhibit 2: Mechanistic Strategies to Treat SMA

Splicing modification	Gene replacement	Muscle activation	Muscle Targeted
Modification of *SMN2* mRNA splicing to increase production of functional SMN protein (nusinersen, risdiplam)	Replacement of faulty *SMN1* gene using viral-vector-based gene therapy (onasemnogene abeparvovec)	Improvement of muscle force-frequency response in skeletal muscle via activation of fast skeletal muscle troponin (reldesemtiv*)	Increased skeletal muscle mass and force via myostatin inhibitor (apitegromab*, taldefgrobep*)

* investigational

sitters with improved standards of care.

The mechanistic strategies to treat SMA are aimed at increasing SMN protein levels, increasing muscle activation which is SMN independent, neuroprotection of the motor neurons affected by loss of SMN protein, and muscle protection to prevent or restore the loss of muscle function in SMA (Exhibit 2). The SMN strategies currently marketed include improving production of functional SMN protein by modification of SMN2 mRNA splicing and gene replacement.[14] Nusinersen and risdiplam target SMN2 splicing modification to improve SMN levels. Gene replacement with Onasemnogene abeparvovec-xioi is replacement of the faulty SMN1 gene using viral-vector-based gene therapy. Exhibit 3 compares the three treatments. Importantly, these agents do not cure SMA but are disease-modifying.

Nusinersen, an antisense oligonucleotide, increases the amount of SMN protein that is produced and has been studied in infantile onset SMA (Type 1), later onset SMA, presymptomatic SMA, and in adults with SMA.[15-20] The trials of SMA therapies all use survival, need for ventilation assistance, and measures of motor function to assess efficacy. In a randomized, double-blind, sham-controlled study of nusinersen in 121 infants (≤ 7 months) with SMA Type I, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (51% versus 0%), and the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; $p = 0.005$).[15] In a multicenter, double-blind, sham-controlled study in 126 patients with later-onset SMA (2 to 12 years), 57 percent of the children in the nusinersen group and 26 percent in the control group had an increase from baseline to month 15 in the Hammersmith Functional Motor Scale-Expanded (HFMSE) score of at least 3 points ($p < 0.001$), and the overall incidence of adverse events was similar in the nusinersen group and the control group (93% and 100%, respectively).[16] Long-term results from the later onset cohorts found benefit out to three years with continued therapy.[17] The pre-symptomatic study was an open-label, single-arm trial of nusinersen in infants with genetically diagnosed SMA (mostly ≤ 1 month at enrollment). At the end of this trial, 25 children were a median 34.8 months of age and past the expected age of symptom onset for SMA Types 1 or 2, all were alive and none required tracheostomy or permanent ventilation.[18] All 25 participants achieved the ability to sit without support, 92 percent achieved walking with assistance, and 8 percent achieved walking independently. Overall, 88 percent of the participants were able to maintain full oral feeds. A meta-analysis of 19 papers reporting motor function in SMA Type 2 and 3 treated with nusinersen found that treatment minimized loss of motor function across a wide range of these patients.[19]

Nusinersen has also been studied in adults with genetically confirmed 5q SMA (aged 16 to 65 years) with a homozygous deletion of exons 7, 8, or both, or with compound heterozygous mutations. Mean motor function scores were significantly increased compared with baseline at six months (mean

Exhibit 3: FDA-Approved Treatments for SMA

FDA-Approved Agent	Nusinersen	Risdiplam	Onasemnogene abeparvovec-xioi
Indication	(2016) all ages 5q SMA	(2020) all ages 5q SMA	(2019) < 2 years old
Administration	Intrathecal every 4 months after 4 loading doses	Oral Daily	Intravenous single infusion
Mech of Action	SMN2 splice modifier	SMN2 splice modifier	SMN1 transgene
Safety/Monitoring	PT, PTT, platelets, Urine protein	Hepatic function, pregnancy test	AST, ALT, bili, PT, platelets, troponin-I
Adverse Events	Post lumbar puncture headache	GI distress, rash, fever, male infertility, teratogenicity	Liver injury, thrombocytopenia, thrombotic microangiopathy

difference 1.73, $p < 0{\cdot}0001$), 10 months (2.58, $p < 0{\cdot}0001$), and 14 months (3.12, $p < 0{\cdot}0001$).[20] Clinically meaningful improvements (≥ 3 points increase) in motor function scores were seen in 28 percent at six months, 35 percent at 10 months, and 40 percent at 14 months. These findings show an important issue with SMA therapies – motor function tends to improve steadily over time. The onset of action is not immediate. Higher than labeled doses of nusinersen are being studied because many adult patients report efficacy wearing off between doses.

Risdiplam is an oral SMN2 splicing modifier designed to increase and sustain SMN protein levels both throughout the central nervous system and peripheral tissues of the body. It has been studied in infants with Type 1 SMA and children and young adults (2 to 25 years old) with Type 2 or 3 SMA and increases SMN levels about two-fold. In addition to the studies included in the FDA submission, risdiplam is being studied in a broad clinical trial program in SMA, with patients ranging from newborns to 60 years of age, including patients previously treated with other SMA therapies.

In a Phase II/III, open-label study of risdiplam in 21 infants aged one to seven months who had type 1 SMA, four infants were in a low-dose cohort and 17 were in a high-dose cohort.[21] The baseline median SMN protein concentrations in blood were 1.31 ng per milliliter in the low-dose cohort and 2.54 ng per milliliter in the high-dose cohort; at 12 months, the median values increased to 3.05 ng per milliliter and 5.66 ng per milliliter, respectively, which represented a median of 3.0 times and 1.9 times the baseline values in the low-dose and high-dose cohorts, respectively. Seven infants in the high-dose cohort and no infants in the low-dose cohort were able to sit without support for at least five seconds. Ninety percent of infants were alive with no permanent ventilation after receiving risdiplam for 12 months. The FDA-approved dosing for this agent is based on age and weight.

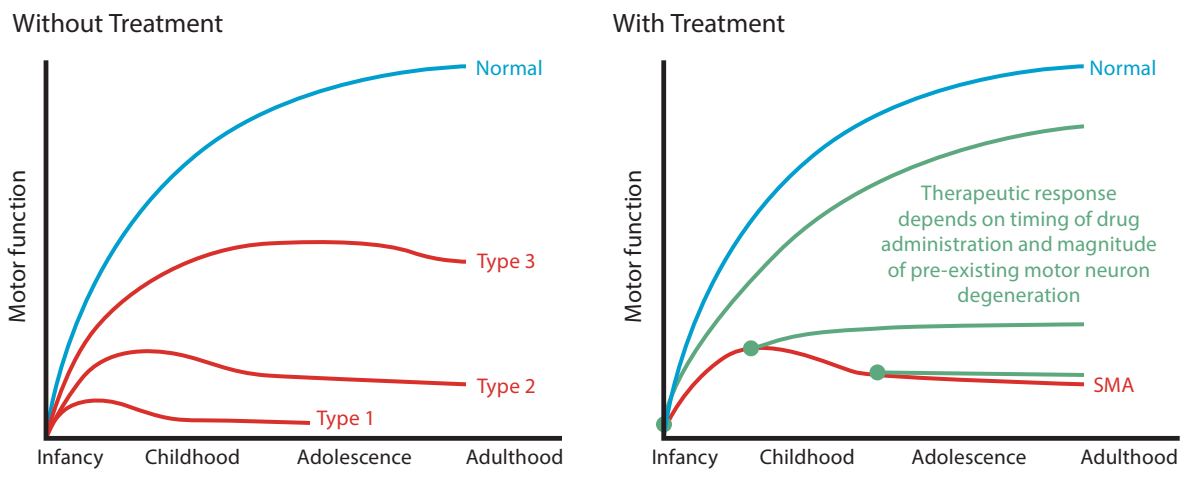
SUNFISH is a Phase III, randomized, double-blind, placebo-controlled study of risdiplam in Type 2 and non-ambulant Type 3 SMA. There was a significantly greater change from baseline in 32-item Motor Function Measure (MFM32) total score with risdiplam compared with placebo at month 12.[22] At month 24 of risdiplam treatment, 32 percent of patients demonstrated improvement (a change of ≥ 3) from baseline in MFM32 total score and 58 percent showed stabilization. Overall, gains in motor function at month 12 were maintained or improved upon at month 24.

Risdiplam is also being studied in patients aged six months to 60 years who have previously received nusinersen, gene therapy, or other investigational agents (JEWELFISH).[23] In preliminary data, significant increases in SMN protein versus baseline was observed at 12 months of therapy. Final data from this trial have not yet been published. Risdiplam has two major advantages – it is orally administered at home rather than requiring an intrathecal injection and it has a lower cost than nusinersen.

Gene transfer therapy was the next iteration in SMA therapy. This therapy is designed to deliver a fully functional human SMN gene into target motor neuron cells leading to production of sufficient levels of SMN protein required to improve motor neuron function. This therapy leads to a rapid onset of effect in addition to sustained SMN protein expression. Within a day of infusion, the SMN levels begin to increase.

Onasemnogene abeparvovec-xioi, an FDA-approved agent, crosses the blood-brain barrier and

Exhibit 4: Clinical Course of Treatment for SMA[29]



targets neurons. It is non-integrating, has a rapid onset of effect, remains stable within the nucleus, and produces sustained SMN expression. The FDA-approved indication is treatment of pediatric patients less than two years of age with SMA with bi-allelic mutations in the SMN1 gene. In the START clinical trial, all 15 patients treated with a single infusion were alive and event-free at 20 months of age, as compared with a historical cohort rate of survival of 8 percent.[24] Of the 12 patients who had received a high dose (3 additional patients received a low dose), 11 sat unassisted, 9 rolled over, 11 fed orally and could speak, and two walked independently. The five-year follow-up report for this trial showed a long-term favorable safety profile up to six years of age and evidence for sustained clinical durability.[25] Of the 10 patients in the high-dose cohort who were followed for five years, all remained alive, without the need for permanent ventilation, and maintained previously acquired motor milestones.

In an open-label, single-arm, single-dose, Phase III trial (STR1VE) in 22 infants (< 6 months) and have spinal muscular atrophy with biallelic SMN1 mutations (deletion or point mutations) and one or two copies of SMN2, gene therapy resulted in 59 percent achieving functional independent sitting for 30 seconds or longer at 18 months of age compared to none of 23 patients in the untreated Pediatric Neuromuscular Clinical Research (PNCR) dataset cohort ($p < 0.0001$).[26] Twenty patients (91%) survived free from permanent ventilation at age 14 months (versus 26%, $p < 0.0001$ in the untreated PNCR cohort). Patients maintained the ability to thrive and achieve motor milestones. There was a rapid and sustained improvement in motor function after dosing.

SPR1NT was a Phase III, multicenter, single-arm study to investigate the efficacy and safety of onasemnogene abeparvovec-xioi for presymptomatic children with biallelic SMN1 mutations treated at six weeks of life or less. Fourteen children with two copies of SMN2, expected to develop Type 1 SMA received gene therapy and were compared with a matched PNCR natural-history cohort (n = 23). All 14 enrolled infants sat independently for up to 30 seconds or more at any visit up to18 months or less ($p < 0.001$; 11 within the normal developmental window).[27] All survived without permanent ventilation at 14 months; 13 maintained body weight (≥ one-third percentile) through 18 months. No child used nutritional or respiratory support. Onasemnogene abeparvovec was effective and well-tolerated for children expected to develop SMA type 1, highlighting the urgency for universal SMA newborn screening.

This gene therapy has also been studied in children between six and 60 months who have three copies of SMN2 and can sit alone for 10 seconds or more, but not stand or walk. Patients were enrolled into one of three (low, medium, and high) dose cohorts and stratified into two groups by age at dosing – younger (6 to 24 months) and older (24 to 60 months).[28] Older patients treated with the medium dose demonstrated increases in HFMSE score greater than commonly observed in natural history.

Onasemnogene abeparvovec-xioi is given as a single intravenous weight-based infusion. Systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) must be given for one day before infusion and continued for a total of 30 days after

administration to dampen or circumvent the expected immune response to the adeno-associated virus viral capsid in the host liver cells. Many times, the corticosteroids will have to be continued for much longer to manage adverse events. This therapy costs $2.1 million along with additional related medical and pharmacy costs of hospitalization for receiving the therapy, follow-up medications, laboratory monitoring, and clinical care.

Taken together, the clinical trial data to date from the three SMA therapies suggest that two related factors affect outcome. The first is age at time of treatment and a trend to better outcome with earlier treatment is clear. The other factor is the extent of pre-existing motor neuron loss (Exhibit 4).[29] Early treatment before onset of motor neuron loss or development of clinical symptoms is ideal. Treatment after onset of weakness constrains achievable responses in a progressive manner. The achievable level of a treatment's clinically meaningful benefit necessarily scales with age and pre-existing disease. All clinicians agree on treating those with three or fewer SMN2 gene copies but treatment of those with four copies of the SMN gene while asymptomatic is controversial but advocated in the guidelines. A multidisciplinary team for clinical care is key to managing those with SMA whether treated with the new therapies or not.

In selecting which disease-modifying therapy to choose, clinicians must consider several factors. There are no head-to-head trials with the three agents. Age is the initial determinant; nusinersen and risdiplam are indicated for all ages and gene therapy is only indicated for those less than two years. It is also important to consider genetic background and SMN2 copy numbers when choosing a therapy. Access to healthcare including proximity to a center with expertise in SMA and managing adverse events of these therapies, transportation to and from the center for medication administration, and insurance coverage impact treatment decisions. For example, with nusinersen, the patient has to have four loading doses at days 0, 15, 30, and 60 and then four doses annually. For someone who lives hours from a treatment center, this can be an insurmountable burden.

Treatment selection also must involve families and adult patients. Families can have unrealistic expectations of treatment – they may expect normal functioning, reversal of disability, and/or rapid improvements. Some providers can also have unrealistic expectations. Provider expectations are based on clinical experience with SMA and its treatment and familiarity with treatment trials. Managing expectations requires providers to clarify personal expectations and patient and family expectations. They must reinforce that any SMA treatment is a disease-modifying therapy and not a cure. Clinicians should be honest and transparent in communications to establish expectations that are realistic and mutual. Agreement and commitment to a treatment plan should include a written overview.

Earlier diagnosis leads to earlier treatment and better outcomes. In order to pay for a therapy, third-party payers want treatment to improve outcomes, reduce overall cost, and provide value. In most cases, third-party payers are covering treatment for patients with up to three copies of SMN2, however, coverage for patients with four copies is harder to achieve.

SMA treatment outcomes include improvement or maintenance of motor function, attainment of developmental milestones, maintenance of oral feeding, appropriate growth, respiratory function, rate of hospitalizations, and stability or improvement in compound motor action potentials. Other outcomes include patient and family perspective, patient energy and fatigue, and quality of life. For example, reducing fatigue can improve performance of activities of daily living. Biomarkers which can be measured to track outcomes are under investigation.

Real-world outcomes data with SMA treatment are beginning to be published. An Australian real-world study of safety and efficacy in 21 children (age range, 0.65 to 24 months) treated with onasemnogene abeparvovec-xioi has been published.[30] Most of these children (90.4%) had previous nusinersen treatment. Transient treatment-related side events occurred in all children – vomiting (100%), transaminitis (57%) and thrombocytopenia (33%). Duration of prednisolone following treatment was prolonged (mean 87.5 days, range 57 to 274 days). Seventy-six percent gained at least one motor milestone. Stabilization or improvement in bulbar or respiratory function was observed in 95.2 percent of patients. A German/Austrian real-world study found similar results in 76 children.[31] Seventy-six percent had received nusinersen previously. In 60 patients with available data, 49 had a significant improvement on the CHOP-INTEND score (≥ 4 points) and HFMSE score (≥ 3 points). Mean CHOP INTEND scores increased significantly in the six months after therapy in children younger than eight months ($p < 0.0001$) and children aged between eight and 24 months ($p < 0.0001$), but not in children older than 24 months (n = 6; $p = 1.00$). In the 45 children pretreated with nusinersen with available data, CHOP INTEND score increased by 8.8 points ($p = 0.0003$) at six months after gene replacement therapy.

Not all patients have a robust response to gene therapy so studies are ongoing to identify the

effects of secondary nusinersen and risdiplam treatment, The RESPOND clinical trial is a Phase IV, open-label, multicenter, single-arm study of nusinersen in patients with SMA (3 years old and younger) previously treated with onasemnogene abeparvovec-xioi who have suboptimal clinical status in one or more of four domains (motor function, abnormal swallowing/feeding ability for age, need for respiratory support, other).[32] The transgene therapy only impacts about 60 percent of motor neurons. Nusinersen has the potential to increase SMN protein in the nonimpacted 40 percent, which may lead to additional clinical benefit for individuals with SMA. Interim efficacy results at six months from 27 of 60 planned study participants show improvements in motor function in most as measured by increased mean total Hammersmith Infant Neurological Examination Section 2 (HINE-2) score from baseline. Participants with two SMN2 copies (n = 24) improved by a mean of over 5 points on HINE-2. All participants with three SMN2 copies (n = 3) improved; a mean change from baseline was not calculated due to the small number of participants. Most participants (25 of 27) with investigator-reported suboptimal motor function at baseline improved.

RESTORE is a prospective, multicenter, multinational observational registry of newly diagnosed SMA patients.[33] Patients will be enrolled over a five-year period and followed for 15 years or until death; patients will be managed according to usual clinical practice. Assessments included in the registry will include SMA history and treatment, pulmonary, nutritional, and motor milestones, healthcare resource utilization, work productivity, activity impairment, adverse events, quality of life, caregiver burden, and survival. Data from this registry will be helpful in identifying short- and long-term outcomes from the SMA specific treatments.

More therapies are under investigation. Muscle directed therapy may further improve motor function. Apitegromab and taldefgrobep are pro-myostatin inhibitors given as IV infusions which prevent myostatin activation leading to increased muscle cell growth. Human clinical trials are currently in progress. Reldesemtiv is a fast skeletal muscle troponin activator which is also being studied for SMA. These non-SMN-modifying therapies will be used in combination with the SNM targeting agents.

Conclusion

Children and family lives are being dramatically improved with the available SMA therapies. Earlier diagnosis of SMA leads to earlier treatment and better outcomes. The magnitude of benefit may depend on SMN2 copy numbers and clinical signs at time of treatment but pediatric and adult patients treated with disease-modifying therapies show benefit. The long-term outcomes of these therapies are beginning to accumulate.

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Innovations in the Treatment and Management of Chronic Cough: Expert Perspectives on the Role of New and Emerging Therapies

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Summary

Refractory or unexplained chronic cough significantly impacts quality of life. Unfortunately, effective therapies are currently lacking, however, at least one new class of medication is on the horizon.

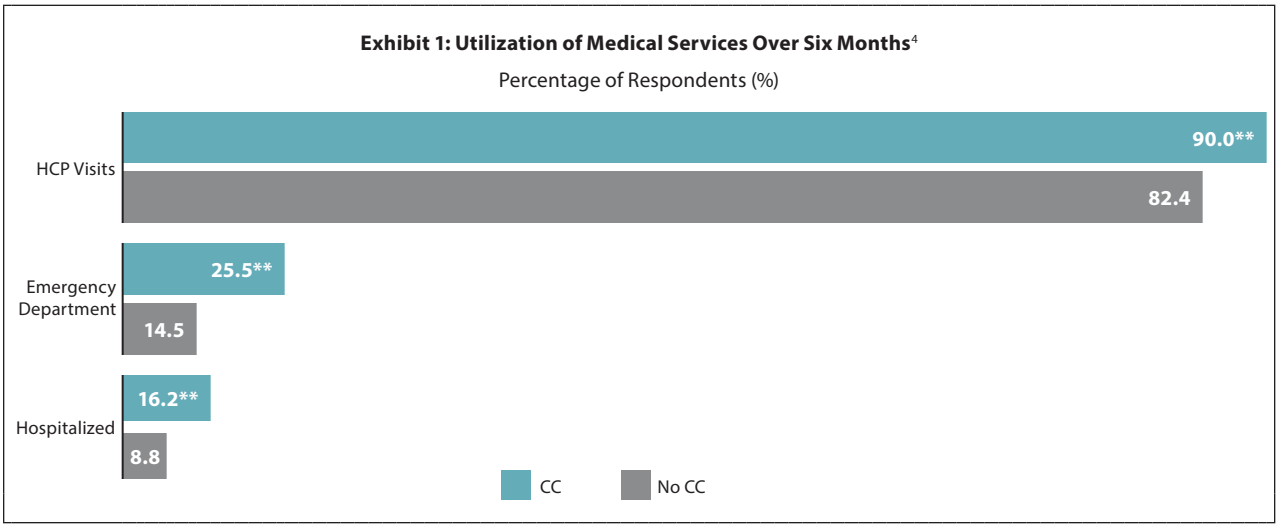
Key Points

- Chronic cough is frustrating for clinicians and patients.
- An extensive workup may be required to rule out treatable causes.
- Present treatments have minimal effect on refractory or unexplained chronic cough.
- Available data suggests that P2X3 antagonists may be beneficial.

COUGH SERVES A REAL PURPOSE IN protecting and clearing the airways but there is a problem when the patient develops a pathologic cough. These patients present stating they have been coughing for months, have seen multiple physicians, and have tried many different treatments with no success.

Cough can be classified as acute, sub-acute, or chronic.[1] An acute cough, primarily due to upper respiratory tract infections, is transient and self-limited, lasting three weeks or less. Acute cough is one of the most common reasons for a healthcare provider visit. A sub-acute cough lasts between three and eight weeks. The most common cause of a sub-acute cough is post-viral infection cough. Pertussis and mycoplasma pneumonitis are other causes. A chronic cough is one which lasts for greater than eight weeks.

Chronic cough occurs in 5 percent to 11 percent of the United States (U.S.) population but the prevalence is closer to 5 percent when smokers are excluded.[2,3] The major problem with chronic cough is its impact on quality of life. In one U.S. based survey, those with chronic cough had lower mean scores on the Medical Outcomes Study 36-item Short Form Survey v2 physical ($p < .001$) and mental ($p < .001$) component summary scores compared to those without cough.[4] More respondents with chronic cough that matched controls experienced severe anxiety and severe depression in the past two weeks, work productivity impairment, impaired sleep quality and daytime sleepiness, as well as more emergency department visits and hospitalizations in the past six months ($p < .001$ for all comparisons).[4] Chronic cough interferes with lifestyle and leisure activities. For example, social activity is limited by cough itself and other people's reaction to coughs. These patients can be expensive to manage because of high rates of healthcare utilization (Exhibit 1).[4] Another factor in the cost of managing chronic



**Statistically significant difference
CC = chronic cough; HCP = health care provider

cough is that each clinician the patient sees for their cough repeats many of the same tests looking for a cause of the cough.

The American College of Chest Physicians has published evaluation guidelines for acute, subacute, and chronic cough in adults.[5] Exhibit 2 shows the chronic cough evaluation algorithm.[5] An extensive workup may be required to rule out treatable causes of cough. The guidelines note that clinicians should always screen for red flags as a clue to a potentially life-threatening condition and environmental/occupational/travel/medication (sitagliptin or angiotensin-converting enzyme inhibitors) factors that might be contributing to the cough. The potential for tuberculosis in endemic areas or high-risk populations should be considered even if chest radiographs are normal. Cough severity and impact on quality of life before and after treatment should be assessed and a follow-up visit scheduled for four to six weeks after the initial visit. Clinicians should consider referral to a recognized cough clinic for patients with refractory or unexplained chronic cough (R/UCC).

Upper airway cough syndrome (UACS), asthma, non-asthmatic eosinophilic bronchitis, and gastroesophageal reflux disease (GERD) account for most cases of chronic cough in immunocompetent, nonsmoking patients with normal chest radiographic findings. The recommended tests to identify these big four causes are shown in Exhibit 2.[5] Therapy is directed to the underlying cause when one is identified or suspected.

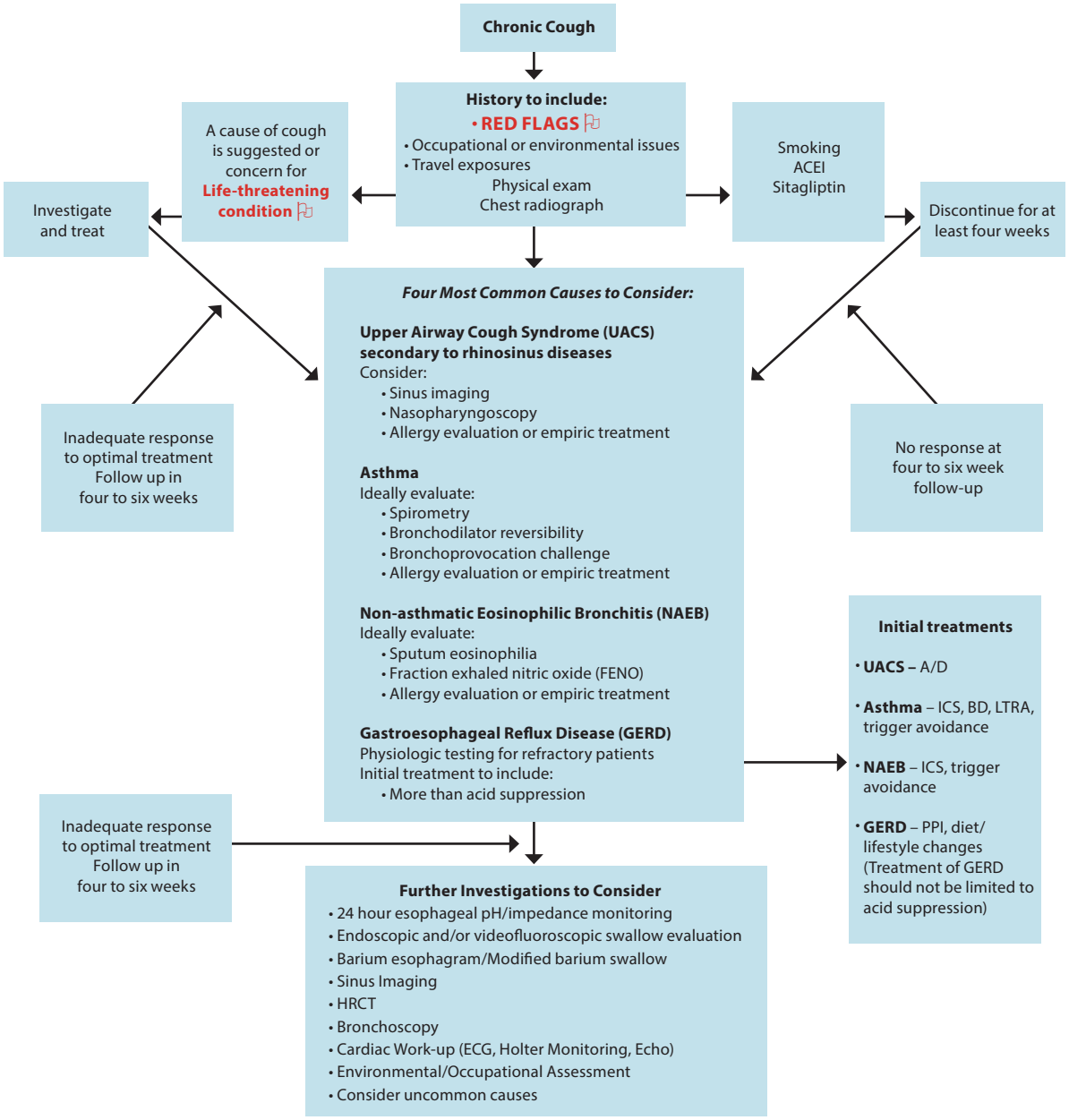
In patients in whom the cause of the UACS induced cough is apparent, such as allergic rhinitis, specific therapy directed at this condition should be instituted. For patients in whom the cause is not apparent but UACS is suspected, empiric therapy should be instituted with a first- generation antihistamine. First-generation antihistamines such as azatadine and brompheniramine plus pseudoephedrine have been shown to be more effective than newer, less-sedating antihistamines because of their drying ability. Patients typically respond within two weeks of initiating therapy but response may sometimes take several months.

For patients with chronic cough due to asthma, the use of inhaled corticosteroids is usually the first-line treatment. In general, inhaled bronchodilators alone, such as albuterol, may not be effective for cough variant asthma. Also, the use of a leukotriene receptor antagonist can be considered. Empiric treatment, for suspected but not proven asthma as cause of cough, is an oral corticosteroid burst and tamper over 10 to 14 days.

Non-asthmatic eosinophilic bronchitis is characterized by the presence of eosinophilic airway inflammation but is not associated with variable airflow limitation or airway hyperresponsiveness like asthma. The diagnosis is made by the confirmation of eosinophilic airway inflammation usually with induced sputum analysis. In patients with chronic cough who have normal chest radiograph findings, normal spirometry findings, and no evidence of variable airflow obstruction or airway hyperresponsiveness, the diagnosis of non-asthmatic eosinophilic bronchitis should be considered. The treatment of choice is inhaled corticosteroids and empiric treatment is the same as with asthma.

The recommended treatment of GERD-related cough is a double dosed proton pump inhibitor for

Exhibit 2: CHEST Guidelines[5]



RED FLAGS

- Hemoptysis
- Smoker > 45 years of age with a new cough, change in cough, or coexisting voice disturbance
- Adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or who have quit within the past 15 years
- Prominent dyspnea, especially at rest or at night
- Hoarseness
- Systemic symptoms
  - Fever
  - Weight loss
  - Peripheral Edema with weight gain
- Trouble swallowing when eating or drinking
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough

ACEI= angiotensin-converting enzyme inhibitor; A/D = antihistamine/decongestant; BD = bronchodilator; HRCT = high-resolution CT; ICS = inhaled corticosteroid; LTRA = leukotriene antagonist; PPI = proton pump inhibitor

at least eight weeks. Healthy weight loss, raising the head of the bed, eating within three hours of bedtime, and lifestyle modifications that include avoiding caffeine, chocolate, fatty foods, spicy foods, peppermint, and alcohol should be instituted. If it appears that the chronic cough is due to GERD, but no better with above, a gastrointestinal consult would be appropriate.

Despite identifying probable causes of cough and treating them, some patients will still have a chronic cough. A refractory chronic cough is defined as associated/underlying medical conditions that are identified and treated per guidelines, but cough persists. For other patients, no apparent cause can be identified which is labeled unexplained chronic cough. Refractory or unexplained chronic cough (R/UCC) occurs more often in women than men and peaks in the fifth and sixth decades of life.[6] It should be considered a disease rather than a symptom such as cough typically is. These patients have a dry or minimally productive cough with cough spasms of 20 to 30 coughs and sometimes they feel like they are going to pass out from the cough. Urinary incontinence is also common in women with R/UCC. R/UCC appears to be a neuronal abnormality which leads to cough hypersensitivity. Cough hypersensitivity is observed with various exposures.[7-9] Triggers that initiate cough may include exposure to aerosols, scents, odors (hypertussia) and laughing, cold air, talking, or singing (allotussia). Those affected report recurring sensations such as "tickle in the throat" and urge to cough.

The treatment options for R/UCC are speech pathology treatment and altering neuronal pathways with medications.[10,11] Speech pathology treatment can provide education, strategies to control cough, vocal hygiene, and psychoeducational counseling but it can be difficult to find a practitioner who is familiar with this type of treatment. This treatment can reduce cough frequency and improve the patient's quality of life but the patient must keep up the techniques to maintain benefit.[12]

Gabapentin, pregabalin, amitriptyline, and low-dose morphine have been tried for R/UCC. Cough suppressants do not work for this particular type of cough. There are no medications currently FDA approved for this indication. Gabapentin is the only agent recommended by the American College of Chest Physicians guidelines for managing R/UCC (up to 900 mg BID).[6] One small trial evaluated gabapentin compared to placebo. Gabapentin significantly improved cough-specific quality of life compared with placebo ($p = 0.004$; number needed to treat of 3.58).[13] Adverse events including sedation, nausea, and fatigue are common with any of the agents which have been tried. General practitioners who have not been able to help the patient can refer them to a specialist or chronic cough center.

Better treatment options for R/UCC are needed. A variety of neuromodulatory pathways have been discovered which are involved in the cough reflex and can be targeted with medications. Sodium-channel blockers, transient receptor potential vanilloid subtype 1 (TRPV1) antagonists, transient receptor potential-melastatin 8 (TRPM8 agonists), neurokinin (NK-1) receptor antagonists, and P2X purinoceptor 3 (P2X3) antagonists have all been under investigation. So far, the sodium-channel blockers, TRPV1 antagonists, and NK-1 receptor antagonists have not been successful in clinical trials. TRPM8 is expressed in many of the sensory fibers innervating the upper airways. AX-8, a topically acting TRPM8 Agonist delivered as an orally disintegrating tablet (ODT) placed on the back of the tongue, is currently in late Phase II trials. Treatment with AX-8 40 mg BID compared to placebo showed a reduction in cough frequency within the first 15 minutes after treatment and lasted for more than four hours.[14] This included a 44 percent reduction in cough frequency over two hours compared to 18 percent with placebo and a 35 percent reduction over four hours compared to 20 percent with placebo. Reduction in cough frequency was seen across patients in the study irrespective of high/low baseline cough frequency, duration of coughing, age, or sex.

P2X3 antagonists are the closest to the market for treating chronic cough. P2X3 receptor channels expressed in sensory neurons are activated by extracellular ATP and have been identified as serving important roles in nociception, sensory hypersensitization, and the cough reflex.[15] Extracellular ATP, released due to inflammation or shearing forces or smooth muscle contraction in airways may be an important mechanism for patients with R/UCC. Binding of extracellular ATP to P2X3 and P2X2/3 receptors on C-fiber creates an action potential. C-fiber activation likely initiates pathologic cough.[16] The P2X3 receptor is located primarily on peripheral neurons, thus also making it a promising therapeutic target in neuropathic conditions. Several P2X3 antagonists are under development. Eliapixant and sivopixant have completed Phase II trials, BLU-5937 has moved to Phase III, and gefapixant Phase III trials have been completed. Development of eliapixant was stopped in 2022 despite promising efficacy data in clinical trials, on what appears to be safety grounds.[17]

In a Phase IIb trial in 390 patients, sivopixant did not demonstrate a statistically significant difference

versus placebo in change from baseline in 24-hour cough frequency. The study authors concluded that a dose of 300 mg has potential for R/UCC, showing the greatest improvements in cough frequency and patient-reported outcomes and dose-related mild-to-moderate reversible taste disturbance.[18] Dysgeusia is a known adverse event of this class of agents because P2X2/3 heterodimers have a significant role in taste. In SOOTHE, a Phase IIb trial of BLU-5937, changes in 24-hour cough frequency over placebo of -21.1, -34.4, and -34.2 percent were observed after 28 days of treatment at 12.5, 50, and 200 mg BID, respectively.[19] Dysgeusia occurred in 6.5 percent or fewer subjects with no loss of taste and no discontinuations due to taste disturbance.

Gefapixant, in this class, is the closest agent to market with a new drug application submitted to the FDA. It demonstrated efficacy and was generally well tolerated, except for dysgeusia in Phase II clinical trials in patients with R/UCC.[20,21] On the basis of Phase II data, two international Phase III, randomized, double-blind, placebo-controlled trials, with treatment durations of up to one year were begun (COUGH-1 and COUGH-2).[22] The trials included 730 and 1,314 participants across placebo, gefapixant 15 mg twice per day, and gefapixant 45 mg twice per day treatment groups. Participants were mostly female (74%), mean age was 59, and the mean cough duration was over 11 years. Gefapixant 45 mg twice per day showed significant reductions in 24-hour cough frequency compared with placebo at week 12 in COUGH-1 (18.5%; $p = 0{\cdot}041$) and at week 24 in COUGH-2 (14.6%; $p = 0{\cdot}031$). Gefapixant 15 mg twice per day did not show a significant reduction in cough frequency versus placebo in either study. The most common adverse events were related to taste disturbance – ageusia (4.9% and 6.5%) and dysgeusia (16.2% and 21.1%). The dropout rates due to adverse events in the 45-mg arms of the two trials were 15 percent and 20 percent, compared to 3 percent and 5 percent in the placebo cohorts. With this agent, the rate of taste issues increases with increasing dose but the optimal dose which reduces cough effectively while minimizing taste issues is not yet known.[23] Taste disturbances occur at a higher rate with gefapixant than what has been reported with other P2X3 agents and this may be because it is not a pure P2X3 receptor antagonist.

In January 2022, according to a press release issued by the manufacturer, the FDA issued a complete response letter, declining to approve a new drug application for gefapixant to treat adults with R/UCC.[24] The FDA requested additional information related to measurement of efficacy, not safety. Also in January 2022, the Japan Ministry of Health, Labor and Welfare approved gefapixant 45 mg tablets for adults with R/UCC.[24]

Conclusion

Chronic cough is a frustrating clinical burden with reduced quality of life in the affected patient population. An extensive workup may be required to look for potential causes which can be treated and present treatments have minimal effect on refractory or unexplained chronic cough. Emerging therapies, especially P2X3 antagonists, show great promise for patients.

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Navigating an Increasingly Complex Treatment Paradigm in the Management of Breast Cancer: Optimizing Clinical and Economic Outcomes with Targeted Therapy

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For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

Significant advances have been made in screening for breast cancer and treatment of many subtypes. One area where treatments had been lacking was metastatic triple negative breast cancer (TNBC). This subtype can now be targeted with several different therapies, in addition to chemotherapy, which should provide advancements in overall survival.

Key Points

- First-line therapy for metastatic TNBC is determined by PD-L1 expression and BRCA mutations.
- Immunotherapy, PARP inhibitors, and antibody drug conjugates are all now treatment options for this disease state.
- Overall survival is likely to continue to increase.

APPROXIMATELY 300,000 CASES OF BREAST cancer are diagnosed annually in the United States (U.S.). Lifetime risk in women is 12.8 percent (Exhibit 1).[1] In the U.S., breast cancer has the highest treatment cost of any cancer accounting for 14 percent of all cancer treatment costs.[2] Total annual medical cost is estimated at $26.2 billion plus $3.5 billion for prescription medications. The amount that patients pay for breast cancer care can vary widely. A typical woman with employer-sponsored coverage who is diagnosed with early-stage breast cancer can expect to pay $5,800 out-of-pocket, including premiums. On average, cancer survivors have annual losses in work productivity (due to missed work-days and employment disability) that are more than $1,000 higher compared to people without a cancer history. Some cancer survivors are not able to return to work, while others report not being able to perform all tasks because of illness or distress.

Screening for breast cancer with mammography reduces deaths, increases life expectancy, detects cancer sooner (when it is easier to treat), increases five-year survival, and reduces healthcare spending.[2] Compared to no screening, screening every two years reduces breast cancer deaths by 26 percent for every 1,000 women screened. Women who are screened every two years can expect to live 1.4 months longer than women who are not screened. Screening has contributed to a 29 percent reduction in the number of women diagnosed with breast cancer that has spread to other parts of the body. Almost 98 percent of women diagnosed with breast cancer at the earliest stage live for five years or more, compared to about 31 percent of those diagnosed at the most advanced stage. Breast cancers diagnosed at an early stage are much less expensive to treat than those diagnosed at a late stage.

Some variations in breast cancer can be seen in

Exhibit 1: Risk of Invasive Breast Cancer[1]

Current Age	Diagnosed with Invasive Breast Cancer
20	0.1% (1 in 1,479)
30	0.5% (1 in 209)
40	1.5% (1 in 65)
50	2.4% (1 in 42)
60	3.5% (1 in 28)
70	4.1% (1 in 25)
80	3.0% (1 in 33)
Lifetime Risk	**12.8% (1 in 8)**

racial and ethnic groups. The median age at diagnosis is slightly younger for African American women (60 years old) compared to Caucasian women (63 years old).[2] African American women have the highest death rate from breast cancer which is thought to be partially because one in five have triple-negative breast cancer (TNBC) – more than any other racial or ethnic group. African American women have a higher chance of developing breast cancer before the age of 40 than Caucasian women, again likely because of the high rate of TNBC. At every age, African American women are more likely to die from breast cancer than any other race or ethnic group. Caucasian, Asian, and Pacific Islander women are more likely to be diagnosed with localized breast cancer than African American, Hispanic, American Indian, and Alaska Native women. Asian and Pacific Islander women have a lower death rate from breast cancer. American Indian and Alaska Native women have the lowest rates of developing breast cancer.

Most breast cancer cases are hormone receptor (HR) positive/human epidermal growth factor receptor two (HER2) negative. HER2 positive disease is the next most common subtype. There are now many different treatments for HR positive and HER2 positive disease. Treatments have been lacking in the past for TNBC which lacks estrogen, progesterone, and HER2 receptors. TNBC accounts for 12 percent of breast cancer cases.

TNBC tends to be diagnosed at a much earlier age, recurrence occurs earlier after surgical removal compared to other subtypes, and survival is lower than with other subtypes.[3] In addition to African American women, TNBC is more likely in those with a breast cancer one or two gene mutation (BRCA1/BRCA2). The five-year relative survival rate with TNBC is 77 percent (2012 to 2018 data).[4]

An issue which has made treatment difficult in the past was the lack of biomarkers such as estrogen receptors to target. Also, TNBC is histologically heterogeneous and there are many types which have different prognosis (Exhibit 2). Biomarkers that can now be targeted in metastatic TNBC (mTNBC) include BRCA1/BRCA 2 mutation, programmed death ligand one (PD-L1) expression and other markers of immunotherapy response (MSI-H, TMB-H), HER2-low expression, and various other mutations such as NTRK and RET which have FDA-approved therapies. The National

Exhibit 2: TNBC is Histologically Heterogeneous

- Invasive Ductal Carcinoma high grade
- Invasive Lobular Carcinoma high grade, pleomorphic
- High grade neuroendocrine
- Metaplastic, high grade
- Myoepithelial carcinoma
- Medullary
- Apocrine
- Adenoid-cystic
- Metaplastic, low grade

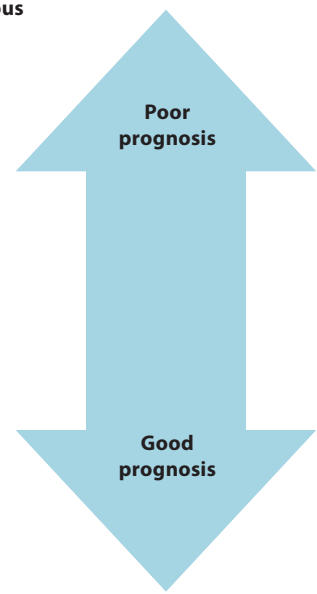

Exhibit 3: Systemic Therapy Regimens for Recurrent Unresectable (Local or Regional) or Stage IV Disease[5]

Setting	Subtype/Biomarker	Regimen
First-Line	PD-L1 CPS ≥ 10 regardless of germline BRCA mutation status	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)(Category 1, preferred)
	PD-L1 CPS < 10 and no germline *BRCA1/2* mutation	Systemic chemotherapy
	PD-L1 CPS <10 and germline *BRCA1/2* mutation	PARPi (olaparib, talazoparib) (Category 1, preferred) Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second-Line	Germline *BRCA1/2* mutation	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan (Category 1, preferred) Systemic chemotherapy
	No germline *BRCA1/2* mutation and HER2 IHC 1+ or 2+/ISH negative	Fam-trastuzumab deruxtecan-nxki (Category 1, preferred)
Third-Line and Beyond	Biomarker positive (i.e., MSI-H, NTRK, RET, TMB-H)	Targeted agents
	Any	Systemic chemotherapy

PD-L1 = programmed death ligand 1; CPS = combined positive score; BRCA = breast cancer; HER2 = human epidermal growth factor receptor two; IHC = immunohistochemistry; ISH = In situ hybridization; MSI-H = microsatellite instability high; NTRK = neurotrophic tyrosine receptor kinase; RET = rearranged during transfection; TMB-H = tumor mutation burden high; PARPi = poly-ADP ribose polymerase inhibitor

Exhibit 4: Testing for *BRCA1/2* Mutations[5]

Patients diagnosed at ANY AGE with breast cancer and any of the following:

- To aid adjuvant therapy decision-making using olaparib in high-risk EBC
- To aid systemic therapy decision-making using PARP inhibitors in the metastatic setting
- TNBC histology
- Lobular breast cancer and personal/family history of diffuse gastric cancer
- Male breast cancer
- ≥ 1 close male relative with breast cancer

Patients with personal history of breast cancer and ≥ 1 of the following:

- Aged ≤ 45 years at diagnosis
- Aged 46 to 50 years at diagnosis, plus any:
  - Family history (unknown or limited)
  - Multiple primary breast cancers at any time interval
  - ≥ 1 close blood relative diagnosed at any age with breast, ovarian, pancreatic, or prostate cancer
- Aged ≥ 51 years at diagnosis plus any of the following:

  ≥ 1 close blood relative aged ≤ 50 years with breast cancer

  ≥ 1 close blood relative diagnosed at any age with ovarian or pancreatic cancer

  Close male relative with breast cancer or high-risk prostate cancer

  ≥ 3 total breast cancer diagnoses in patient/close blood relative

  ≥ 2 blood relatives with breast cancer or prostate cancer
- Ashkenazi Jewish ancestry

Comprehensive Cancer Network (NCCN) Guideline recommendations for treating mTNBC are shown in Exhibit 3.[5] It is important to note that the systemic treatment of advanced or metastatic disease may prolong survival and enhances quality of life (QOL) but is not curative.[5] Therefore, treatments associated with minimal toxicity are preferred.

First-line therapy for mTNBC is determined by PD-L1 expression and germline BRCA mutations. For PD-L1 combined positive scores greater than or equal to 10 regardless of BRCA status, pembrolizumab plus carboplatin-based doublet chemotherapy is the NCCN preferred regimen. TNBC is more likely than other breast cancer subtypes to benefit from immune checkpoint blockade therapy due to its higher immunogenicity, higher enrichment by tumor-infiltrating lymphocytes, and higher levels of PD-L1 expression.[6] Better results are seen when immunotherapy is given as first-line treatment than when given in later lines of treatment for mTNBC.

Germline BRCA (gBRCA) mutations may occur in both TNBC and HR+/HER2- subtypes. About 14 percent of those with TNBC and 5 percent with HR+/HER2- have gBRCA mutations.[7] BRCA is involved in repairing breaks in double-stranded DNA though homologous recombination.[8] If BRCA1 or BRCA2 are mutated, damaged DNA may not be repaired properly, and damaged cells can multiply out of control leading to various cancers. Universal screening for these mutations has not been shown to be cost effective so selective screening is recommended.[9] Exhibit 4 outlines which patients should be tested for gBRCA mutations.[5]

Poly-ADP ribose polymerase (PARP) is involved in base-excision repair. Cells with BRCA mutations have nonfunctional homologous recombination but can repair DNA through base-excision repair (non-homologous repair). PARP inhibitors prevent repair of breaks in single-stranded DNA and induce synthetic lethality in cells deficient in homologous recombination.[10] Two PARP inhibitors, olaparib and talazoparib, are FDA approved for treating metastatic gBRCA mutated breast cancer.[11,12] For mTNBC, they are a first-line option in those with gBRCA mutation who are not candidates for checkpoint immunotherapy based on PD-L1 expression. They are the preferred therapy for second-line therapy in those who have gBRCA mutation. The NCCN Guidelines recommend germline testing on all metastatic breast cancer patients to determine if they could be a candidate for a PARP inhibitors.[5] While olaparib and talazoparib are FDA indicated in HER2-negative disease, the NCCN Panel supports use in any breast cancer subtype associated with gBRCA1/2 mutations.[5] Olaparib is also used in earlier stages of TNBC as adjuvant therapy in those with gBRCA mutations. PARP inhibitors are being studied in combination with chemotherapy, in combination with immunotherapy, and for treatment in those with other homologous recombination pathway gene mutations other than BRCA1/2.

Another biomarker that can be targeted in mTNBC is Trop-2, a transmembrane calcium signal transducer, which is highly expressed in TNBC and plays a role in tumor growth and progression. Sacituzumab govitecan is an antibody drug conjugate (ADC) that targets Trop-2 and delivers govitecan chemotherapy directly into cancer cells. Progression-free and overall survival were significantly longer with sacituzumab govitecan than with single-agent chemotherapy among patients with mTNBC.[13]

Another advance in the treatment of mTNBC is the approval of fam-trastuzumab deruxtecan (an HER2-directed antibody-drug conjugate already FDA approved for HER2 positive disease), for HER2-low disease. The HER2-low category includes those who have borderline immunohistochemistry (IHC) scores of 1+ and 2+; HER2-positive is defined as a score of 3+.[14] In situ hybridization (ISH) is also negative in HER2-low disease. Studies have found rates of HER2-low in TNBC from 21 to 36 percent.[15] In the DESTINY-Breast04 trial, patients with previously treated HER2-low metastatic breast cancer who were treated with fam-trastuzumab deruxtecan had significant improvements in survival compared to those treated with chemotherapy alone.[16] The median OS was 23.9 months and 17.5 months, respectively (HR for death, 0.64; $p = 0.003$). Based on this study, this agent is now FDA approved for adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH -) breast cancer, as determined by an FDA-approved test, and who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

Future therapies for TNBC under investigation are numerous. Capivasertib and ipatasertib are AKT inhibitors being studied in combination with chemotherapy and immunotherapy. Toripalimab and carelizumab are additional investigational immunotherapies.

Conclusion

First-line therapy for metastatic TNBC is determined by PD-L1 expression and BRCA mutations. Immunotherapy, PARP inhibitors, and antibody drug conjugates are all now treatment options for this disease state. Overall survival is likely to continue to increase with these therapies and additional therapies on the horizon.

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Best Practices in the Treatment and Management of HIV: An In-Depth Look at ART Decision Making Strategies for Optimized Clinical and Economic Outcomes

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Summary

The management of HIV infection continues to evolve. Today most people with HIV are started on a single daily dose of antiretroviral combinations which are highly effective in achieving undetectable viral levels. There are also effective regimens for preventing infection in those who are high-risk.

Key Points

- Aging with HIV infection is associated with an increased risk of common comorbidities.
- Currently recommended initial regimens are highly effective with low rates of treatment failure.
- Switching therapy is important to simplify regimens and avoid toxicities and drug-on-drug interactions.
- Effective therapy reduces costs, no matter which regimen is used.
- Improving outcomes in HIV care should target adherence, connection, and retention in care.

APPROXIMATELY 1.2 MILLION PEOPLE IN THE United States (U.S.). are living with HIV infection.[1] About 13 percent of them do not know it and need testing. Over 36,000 new cases were diagnosed in 2021 (the most recent year with available data). HIV continues to have a disproportionate impact on certain populations, particularly racial and ethnic minorities, gay people, bisexuals, and other men who have sex with men (MSM). Men accounted for 79 percent of new diagnoses in 2021 and MSM account for 67 percent of the new cases. With diagnosis and appropriate treatment, the death rate from HIV has dramatically declined.

All cases of HIV should be treated – years ago treatment was withheld until the disease showed progression. The basic principles of treatment are shown in Exhibit 1. Overall, the goal of therapy is to obtain and maintain undetectable HIV levels. Rapid initiation of antiretroviral medications (ARVs) increases likelihood of therapy continuation, patient retention in care, and viral suppression at 12 months.[2]

There are 25 different antiretroviral agents available for treating HIV. Most recently, lenacapavir (a first-in-class HIV capsid inhibitor), was approved by the FDA in December 2022. Because therapy continues to evolve, the guidelines for managing HIV are living documents which should be consulted frequently for changes.[3] The guidelines cover diagnosis, initiating therapy, disease and medication monitoring including recommended frequency, adjusting therapy if undetectable levels are not achieved, and managing multidrug resistance among other topics.

Several regimens are recommended for initial treatment of naïve patients (Exhibit 2).[3] Because some people at risk for HIV are now taking

Exhibit 1: HIV Treatment Basic Principles

- Everyone with HIV should be treated
- The goal of treatment is to reduce the HIV viral load to undetectable levels (< 50 copies/mL)
- People with undetectable viral loads do not get HIV related infections and malignancies
- People with undetectable viral loads do not transmit their infection to their sexual partners [U(undetectable) = U (untransmissible)]
- Patients are often started on therapy within a week of their diagnosis
  - Goal is to achieve an undetectable viral load as rapidly as possible
  - Treatment is begun before all lab tests have returned

preventive ARV agents [pre-exposure prophylaxis (PrEP)] starting therapy requires consideration of which PrEP regimen has been used. The first three regimens are single-dose, once-a-day regimens. Bictegravir/tenofovir alafenamide/emtricitabine is the most used option. Once daily regimens have led to an enormous reduction in patient burden compared to some of the older regimens.

Despite the success of combination ARV therapy in achieving durable virologic suppression and preventing AIDS and its devastating consequences, people with HIV are at increased risk for multiple comorbidities associated with aging, including cardiovascular disease (CVD), lung disease, liver disease, kidney disease, diabetes, neurocognitive disorders, decreased bone mineral density, malignancies, and other diseases.[4] Evidence suggests that treated HIV infection is associated with accentuated aging phenotypes, however, these age-related comorbidities can occur at younger ages.[5,6] Depending on the agents used, HIV treatment can also lead to weight gain, hyperlipidemia, hypertension, renal disease, diabetes, and osteopenia/osteoporosis. For example, weight gain is associated with integrase inhibitors (dolutegravir, bictegravir, elvitegravir, raltegravir). Weight gain is accentuated when tenofovir alafenamide is used in combination with integrase inhibitors. The weight gained is distributed across limbs and trunk and the clinical consequence of this weight gain is uncertain. Weight gained is not easily lost with a switch to an alternative regimen and it happens shortly after starting or switching therapies. If a person with HIV already has some of these comorbidities or is at high-risk for one, certain ARVs will need to be avoided.

There are many reasons changes may need to be made to therapy. Lack of efficacy or development of resistance and adverse events are common issues. Nonadherence may be the cause for these issues. Switching to a single-daily-dose regimen for patients on multiple-dose regimens will improve patient convenience and will improve medication adherence. Additional patient support and/or more frequent healthcare visits may be needed to improve adherence. For those who do not wish to take daily medication, there is a long-acting injectable option discussed later. New drug-on-drug interactions may also prompt a therapy switch. For example, if the patient requires proton pump inhibitors, rilpivirine and atazanavir need to be avoided. Pregnancy is another consideration for potentially switching agents.

In considering which regimen to switch to, clinicians must review the patient's treatment history and results of resistance tests. If there is no history of resistance, switching to a standard three-drug regimen will be effective. If there is a history of resistance, switching within a class to a combination with a higher genetic barrier to resistance will be effective. If there is a history of resistance, some two-drug combinations may not be reliably effective.

Long-acting injectable cabotegravir and rilpivirine is a two-medication regimen indicated as a complete regimen for the treatment of HIV infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV RNA less than 50 copies per mL), on a stable ARV regimen, with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. This regimen is equivalent to once daily oral regimens.[7,8] Injectable therapy is given as every one- or two-month intramuscular injections (each medication requires a separate injection) after an initial oral lead-in regimen.

Several therapies have been approved for use with other ARVs for highly treated experienced

Exhibit 2: Regimen Recommendations for Initial ART[3]

For people who do not have a history of cabotegravir long-acting use as a PrEP, the following regimens are recommended:*
Bictegravir/tenofovir alafenamide[TAF]/emtricitabine
Dolutegravir/abacavir/lamivudine**
Dolutegravir/lamivudine
Dolutegravir plus emtricitabine or lamivudine plus TAF or tenofovir disoproxil fumarate (TDF)

* For people with HIV and a history of cabotegravir long-acting use as a PrEP, INSTI genotypic resistance testing should be performed before the start of ART. If treatment is begun prior to results of genotypic testing, the following regimen is recommended – darunavir/cobicistat or ritonavir with TAF or TDF plus emtricitabine or lamivudine (pending the results of the genotype test).

** If HLA-B*5701 negative

(HTE) patients with multidrug resistance (MDR). Fostemsavir is a first-in-class attachment inhibitor given orally twice-a-day. After enzymatic activation to the active molecule temsavir, it binds to gp120 which prevents viral entry into CD4 cells, effectively stopping viral replication of the HIV virus. This agent has been shown to have long-term efficacy and safety in this difficult to treat population.[9]

Lenacapavir is a first-in-class HIV capsid inhibitor approved in late 2022 for HTE patients with MDR. Interestingly, this agent is started with both oral and subcutaneous loading doses and then subcutaneous doses are given every six months. Future treatment options are long-acting lenacapavir with other injectable long-acting agents to form a complete regimen as a long-acting option for those who are not HTE or with MDR.

It would be better to prevent HIV infection rather than having to treat the disease. One strategy to reduce the rate of new HIV infections is the use of a PrEP, in those who are HIV negative but engage in risk behavior, to prevent HIV acquisition. It is currently recommended for MSM, transgender women, and cisgender women who have sex with men who are at risk for HIV infection based upon HIV status of their partners and sexual risk behaviors.[10] FDA-approved products for PrEP are tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) in combination with emtricitabine (each is available as single daily-dose orals) and long-acting injectable cabotegravir every two months (after two initial one month apart injections). Use of these significantly reduces risk of HIV infection in high-risk populations (69% to 90%) when the medications are taken as prescribed (rates depend on the population studied and the particular regimen used).[11-14] Reduction in HIV incidence directly mirrors medication adherence. In selecting which regimen to use for PrEP, cabotegravir injections may be especially appropriate for patients with significant renal disease, those who have had difficulty with adherent use of an oral PrEP, and those who prefer injections every two months to an oral PrEP-dosing schedule.[10]

People living with HIV who achieve and maintain undetectable viral levels rarely get HIV-related complications that require hospitalization. Avoiding hospitalization and complications of therapy are the major opportunities to save costs in HIV care. Importantly, effective therapy has been shown to reduce costs. Failure to link and retain people in care in the U.S. is the main obstacle to successful outcomes of HIV treatment. For many, social and adherence support is critical for treatment success. Missing doses leads to resistance as well as loss of immunologic benefit.

The regimens for HIV range in monthly cost from $1,000 to $4,000 depending on the regimen and whether it is generic. Most people with HIV do not pay for their ARV medications. Medical assistance and Ryan White/AIDS Drug Assistance programs pay for medications for many. Copay cards issued by manufacturers make up the difference between costs covered by insurance or Ryan White Assistance programs support. There is minimal incentive to use generics unless copays are eliminated. Generics and less expensive combinations might be able to replace more expensive agents in some situations.

Conclusion

People with HIV infection are living longer and aging with HIV infection is associated with an increased risk of common comorbidities. The currently recommended initial regimens are highly effective with low rates of treatment failure. Switching therapy is important to simplify regimens and avoid toxicities and drug-on-drug interactions. Overall, effective

therapy reduces costs no matter what regimen is used. Linking people with HIV to care and retaining them in care is the best way to improve outcomes in HIV treatment in the U.S. New treatment strategies and new drugs continue to be developed.

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Evolving Treatment Strategies in the Management of Hyperkalemia: Managed Care Considerations for Improved Clinical and Economic Outcomes

Gary M. Owens, MD

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Summary

Hyperkalemia, especially chronic elevated potassium, is a common problem in patients with certain diseases. Although dietary changes and diuretics can have an impact, many people will require additional therapy with potassium binders which may allow patients to maximize their current disease medications.

Key Points

- Significant hyperkalemia is a major issue in patients with diabetes, chronic kidney disease, and heart failure, especially those taking medications which increase potassium levels.
- The newer potassium binders generally are safer and better tolerated than the older treatment options.
- The newer agents may allow patients to remain on target doses of medications which benefit their underlying disease(s).

HYPERKALEMIA IS A POTENTIALLY LIFE-threatening condition in which serum potassium exceeds 5.5 mmol/L. It can be caused by reduced renal excretion, excessive intake, or leakage of potassium from the intracellular space. Symptoms are non-specific and related to muscular or cardiac dysfunction. Hyperkalemia can be acute or chronic. Acute renal failure, rhabdomyolysis, tumor lyis syndrome, hemolysis, and massive transfusions are some causes of acute hyperkalemia.[1] Treatment of acute hyperkalemia must be initiated immediately using different therapeutic strategies to increase potassium shift into the intracellular space or to increase elimination, together with reduction of intake. Chronic renal failure is the most common disease-related cause of chronic hyperkalemia. A reduced glomerular filtration rate (GFR, especially < 15 ml/min/1.73 m2) with low urine output results in decreased renal excretion of potassium.

Medications interfering with urinary potassium excretion also lead to reduced renal excretion. Those of special clinical relevance are potassium-sparing diuretics (amiloride, triamterene), cyclosporine, and trimethoprim.[2] Non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor inhibitors (ARBs), can cause a decrease in aldosterone and GFR and thereby lead to hyperkalemia.[3] Mineralocorticoid receptor antagonists (MRAs) – spironolactone, eplerenone, finerenone – block the effects of aldosterone leading to sodium excretion and potassium retention. Combined treatment with MRA and ACE inhibitors, especially in patients with renal impairment or heart failure, must be monitored very carefully.[4] Exhibit 1 presents a list of the most common medication offenders and their mechanism.[1,5]

Hyperkalemia may also result from a

Exhibit 1: Many Commonly Used Medications Can Cause Hyperkalemia[1,5]

Drug	Mechanisms
Amiloride	Blocking of sodium channels of luminal membrane of principal cells.
Spironolactone, Eplerenone, Finerenone	Mineralocorticoid receptor antagonist (competing with aldosterone). Inhibition of adrenal aldosterone biosynthesis.
Cyclosporine, Tacrolimus	Inhibition of adrenal aldosterone biosynthesis. Induction of chloride channel shunt. Increasing potassium efflux from cells.
Trimethoprim, Pentamidine	Blocking of sodium channels of luminal membrane of principal cells.
NSAIDs	Induction of hyporeninemic hypoaldosteronism through inhibiting renal prostaglandin synthesis.
ACE inhibitors, Angiotensin-II receptor antagonists	Reduction in adrenal aldosterone biosynthesis through interrupting renin-aldosterone axis. Reduction in effective glomerular filtration rate.
Beta blockers	Inhibiting renin secretion. Decrease in cellular potassium uptake.
Calcium channel blockers (Nifedipine)	Inhibition of adrenal aldosterone biosynthesis.

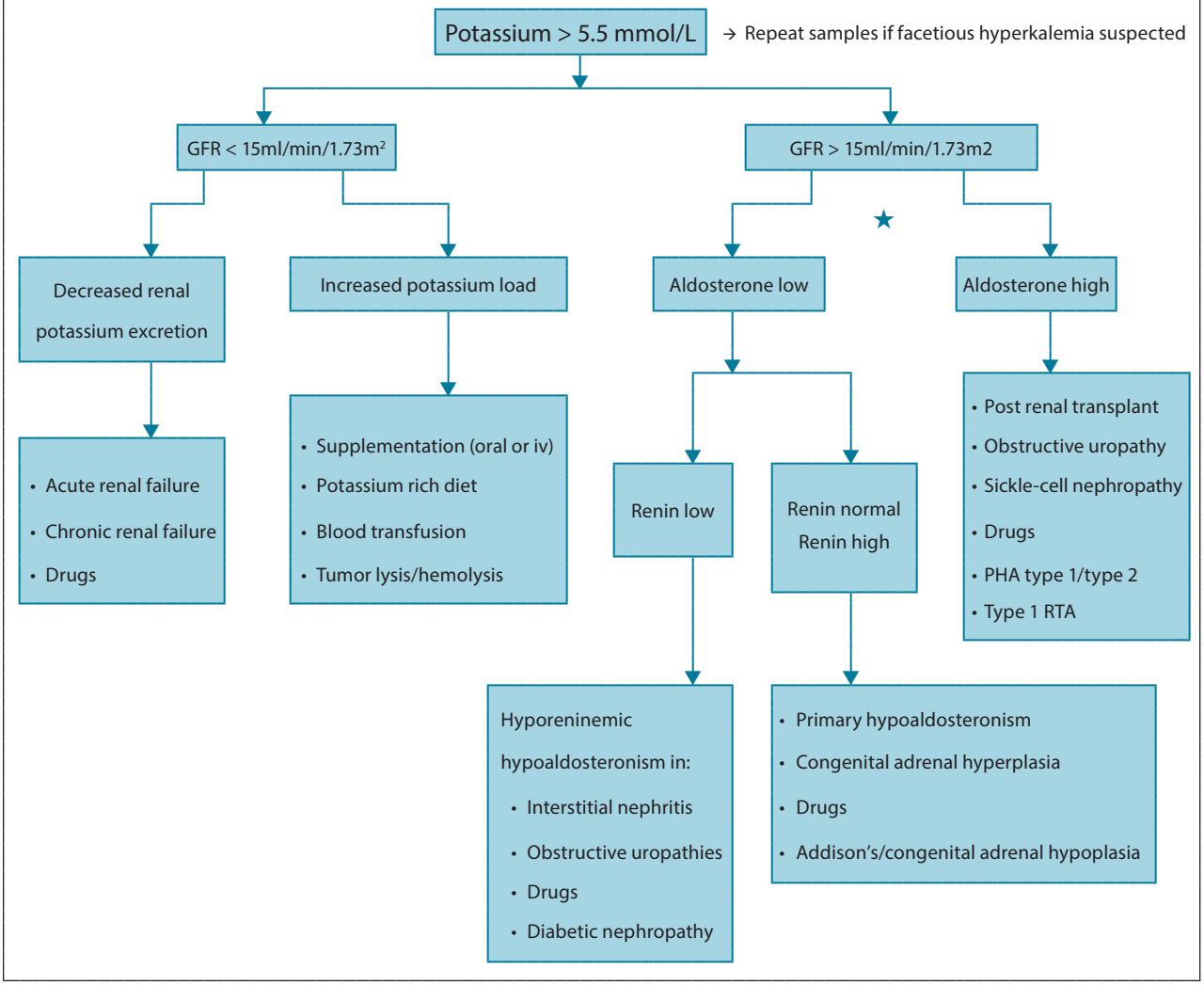
maldistribution between intra- and extracellular space. Mineral acidosis is more likely to cause a shift of potassium from intracellular space into extracellular space than organic acidosis. Reduced insulin levels in diabetes mellitus lead to accumulation of potassium in the extracellular space. Acute increase in osmolality, secondary to hyperglycemia or mannitol infusion, causes potassium to exit from cells. Succinylcholine, especially when given to patients with burn injuries, immobilization, or inflammation, can also lead to hyperkalemia.[6] Hyperkalemic periodic paralysis is a rare condition with mutations of the muscular sodium channel, resulting in paralytic episodes associated with elevated potassium levels.

The most serious manifestations of hyperkalemia are muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias. Hyperkalemia has depolarizing effects on the heart, causing shortened action potentials, and increasing the risk of arrhythmias. The rate of increase in potassium concentrations is important. A rapid increase in serum levels, as with acute hyperkalemia, is more likely to result in cardiac abnormalities than a slow steady rise seen in chronic hyperkalemia. There are differences in tolerable potassium levels among patients. In patients with chronic kidney disease (CKD), compensatory mechanisms may result in tolerance to elevated serum levels.[7] The risk of mortality, cardiovascular morbidity, progression of CKD, and hospitalization is increased in patients with hyperkalemia, especially those with CKD, heart failure (HF), and diabetes.[8] A U-shaped correlation occurs between serum potassium and overall mortality risk because very low potassium levels also increase risk of death.[9]

The exact incidence of hyperkalemia in the general population is unclear. The frequency of hyperkalemia may vary according to the case mix of the studied population, such as a CKD population, by GFR level, and by medications used. A study using Medicare data found a hyperkalemia prevalence between 2.6 percent and 2.7 percent among the overall Medicare population.[10] It was much higher among patients with CKD and/or heart failure (8.9% to 9.3%). Patients with hyperkalemia had a significantly higher economic burden compared with matched patients without hyperkalemia.

Another trial compared economic burden for Medicare and commercial payers.[11] The prevalence of hyperkalemia in the Medicare and commercially insured samples was 2.3 percent and 0.09 percent,

Exhibit 2: Diagnostic Algorithm[1]



★ Calculating TTKG +/- administration of fludrocortisone may help in distinguishing patients who have mineralocorticoid deficiency versus mineralocorticoid resistance.

respectively.[11] Hyperkalemia was associated with multiple comorbidities, most notably CKD. The prevalence of CKD in the Medicare and the commercially insured members with hyperkalemia was 64.8 percent and 31.8 percent, respectively. After adjusting for CKD severity, the annual mortality rate for Medicare patients with CKD and hyperkalemia was 24.9 percent versus 10.4 percent in patients with CKD without hyperkalemia. The costs in patients with CKD and hyperkalemia in the Medicare and commercially insured cohorts were more than twice those in patients with CKD without hyperkalemia.

When a patient is found to have hyperkalemia, the cause needs to be identified in order for best treatment to be chosen (Exhibit 2).[1] Therapeutic strategies should be individualized, taking into account the degree and the cause of hyperkalemia and acute versus chronic state. Chronic hyperkalemia typically requires long-term treatment. Long-term treatment is the focus of the remainder of this article. The options for chronic hyperkalemia include dietary management, management of renin-angiotensin-aldosterone system inhibition (RAASi) medications, diuretics, sodium bicarbonate, and potassium binder therapies. RAASi medications include ACEi, ARBs, and MRAs.

Dietary management of hyperkalemia is difficult for patients. Evidence indicates that a low-potassium diet should be initiated when serum potassium is persistently 5.5 mmol/L or there are additional risk factors, such as CKD at Stage 3b or lower in conjunction with an ACEi or ARB.[12-13] It is impossible (and unhealthy) to have a potassium-free diet. Elevated levels of potassium are found

Exhibit 3: Potassium Binder Therapy Compared[21]

	Sodium Polystyrene Sulfonate (SPS)	Patiromer Sorbitex Calcium	Sodium Zirconium Cyclosilicate
Mechanism of Action	Binds potass0ium in the gastrointestinal tract and facilitates excretion in the feces.	Binds potassium throughout the gastrointestinal tract but predominantly in the distal colon where the concentration of free potassium is highest in exchange for calcium, and facilitates excretion in the feces.	Entraps potassium in the intestinal tract in exchange for sodium and hydrogen, and facilitates excretion in the feces.
Selectivity for Potassium Ions	Non-selective. Also binds calcium and magnesium.	Selective. Also binds magnesium.	Highly selective, nine times the binding capacity of SPS, also binds ammonium.
Sodium Content	1,500mg per 15g dose	No sodium	800mg per 10g dose
Sorbitol Content	15g dose given in 20g sorbitol	4g per 8.4g dose	No sorbitol
Onset of Effect	Variable (hours to days)	4 to 7 hours	1 hour

in a wide range of staple foods and inappropriate restriction results in reduced dietary variety and fiber consumption.[14]

Most patients who develop hyperkalemia while on RAASi agents require those medications for risk reduction and management of multiple comorbidities including hypertension, CKD, HF, and/or diabetes. Stopping these agents is possible but not optimal. Reductions in doses will sometimes improve potassium levels but are not optimal if it means the patient is not receiving a target dose (i.e., evidence-based dosing for the indicated disease). Sometimes adding a potassium depleting diuretic may be an option. A large Canadian study showed worse cardiovascular disease and overall mortality in CKD if RAASi were stopped.[15] RAASi are evidence-based therapies that slow the progression of CKD. In the case of HF and hyperkalemia, since potassium plays a major role in cardiac excitability and arrhythmias, dyskalemia is an important clinical problem that is associated with significant life-threatening complications, however, RAASi are important components of HF treatment.[16] Novel potassium-binding drugs, such as patiromer and sodium zirconium cyclosilicate, may help to optimize therapy in CKD and HF and achieve guideline-recommended doses of RAASi.

After dietary changes and medication modifications, many patients will require potassium binders to manage their potassium levels. In healthy subjects, the gastrointestinal tract contribution to potassium excretion is minimal (about 10% of the total). In the case of CKD, it may increase until it accounts for 50 percent of the total potassium excretion in patients on dialysis.[17]

All of the potassium binders used for hyperkalemia management are non-absorbed and consist of a counter-ion that is exchanged for potassium. This facilitates the elimination of bound potassium in feces. Available agents include sodium polystyrene sulfonate, patiromer sorbitex calcium, and sodium zirconium cyclosilicate.

The oldest agent, sodium polystyrene sulfonate (SPS) is nonselective for potassium and also binds calcium and magnesium ions. Approved in 1958, it can be given orally or rectally and is high in sorbitol (20,000 mg/15g dose) and sodium (1,500mg/15g dose). The high sodium content can be an issue when this agent is used long-term in patients who need sodium restriction. The onset of action is variable (hours to days). Adverse events are mostly gastrointestinal (GI) – abdominal discomfort, constipation, diarrhea, nausea, and flatulence. Clinical studies supporting its long-term use in patients with hyperkalemia are lacking and short-term efficacy is inconsistent.[18]

A significant increase in the incidence of hospitalization for serious adverse GI events has been described in a large cohort of older SPS users when compared with matched non-users.[19] SPS initiation in adults with CKD has been associated with a higher incidence of severe GI adverse events, mainly ulcers and perforations, possibly in a dose-

dependent manner and possibly related to the high sorbitol content.[20]

Patiromer sorbitex calcium provides potassium binding in exchange for calcium ions in the GI tract. It is nonselective, also binds sodium and magnesium like SPS, and was FDA approved in 2015. The onset of action is seven hours and the product contains no sodium. It does contain 1.6g of calcium per 8.4g-dose and 4,000mg of sorbitol per 8.4g-dose. It causes similar GI adverse events to SPS and has been noted to cause hypomagnesemia.

Sodium zirconium cyclosilicate (SZC), approved in 2018, provides potassium binding in exchange for hydrogen and sodium in the GI tract. Its action is in the small and large intestine. It is the most selective for potassium but also binds ammonium. It contains no sorbitol, 800 mg of sodium per 10gm dose, and has an onset of action of one hour. Similar GI adverse events to the other potassium binders occur with this agent and mild-to-moderate edema which appears related to the sodium content has been reported. Exhibit 3 compares the three agents.[21]

In short- and long-term studies involving patients on concomitant RAASi therapy, both SZC and patiromer significantly lowered plasma potassium compared to placebo.[22] In a 2017 meta-analysis that included three trials comparing patiromer with placebo, patiromer decreased serum potassium by 0.70 mEq/L after four weeks of treatment.[23] In the same analysis, three trials comparing SZC with placebo evaluated more acute changes in potassium and found a 0.17 mEq/L decrease at one hour and a 0.67mEq/L decrease at 48 hours. More patiromer treated patients than SZC-treated patients discontinued therapy due to an adverse event (8% versus 1%). The newer potassium binders are more expensive than SPS but cost-effectiveness studies are needed in this category.

Patiromer and SZC can effectively and safely correct hyperkalemia and maintain normokalemia in patients with co-morbidities receiving RAASi therapy whereas long-term use of SPS has been associated with severe GI adverse events resulting in hospitalization. The long-term efficacy and safety of these newer agents remains to be ascertained. However, their use for cardiovascular and renal risk reduction in combination with RAASi therapy holds promise for renal and cardiovascular protection in non-CKD patients.

Conclusion

Hyperkalemia is a common clinical problem. Significant hyperkalemia is a major issue in patients with diabetes, CKD, and HF, especially in those taking RAASi. Recent advances have expanded the therapeutic options for treating these patients. The newer potassium binders generally are safer and better tolerated than the older treatment option. Chronic hyperkalemia management often requires cessation of RAASi, but newer oral binding medications may provide some opportunity for stable and well tolerated long-term control.

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Changing the Treatment Landscape for Prostate Cancer: Moving Towards Improved Outcomes

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Summary

The management of metastatic prostate cancer continues to evolve. Recent developments include a significant change in the standard of care for first-line treatment in those with hormone sensitive disease and newly approved combinations in castrate resistant disease. Additionally, a radioligand has been approved for selected patients with castrate resistant disease.

Key Points

- Androgen deprivation therapy (ADT) alone is no longer the standard of care for most patients with metastatic hormone sensitive prostate cancer (mHSPC).
- All patients with mHSPC should receive an androgen receptor pathway inhibitor (ARPI) and possibly docetaxel in conjunction with ADT to improve survival.
- Poly-ADP ribose polymerase (PARP) inhibitors have demonstrated efficacy in mCRPC and will be used in combination with ARPI.
- Lutetium Lu 177 vipivotide tetraxetan improves progression-free and overall survival in patients with PSMA PET-positive mCRPC.

THE AMERICAN CANCER SOCIETY'S estimates for prostate cancer in the United States for 2021 are 288,300 new cases of prostate cancer and 34,700 deaths.[1] About 1 in 8 men will be diagnosed with prostate cancer during their lifetime and risk increases with age.[2] The overall five-year survival rate for this cancer has increased significantly since the late 1970s' from 68 percent to 97 percent but remains poor for metastatic disease at 32 percent.[3]

With metastatic disease, treatment is selected based on whether the disease is hormone sensitive or resistant. All prostate cancers initially respond to androgen deprivation therapy (ADT) but over time become resistant. One of the more dramatic changes in prostate cancer management has been in metastatic hormone sensitive prostate cancer (mHSPC). The prior standard of care for mHSPC was ADT alone but this has been found to result in poor clinical outcomes. There is now compelling evidence that treatment intensification by early addition of either docetaxel, an androgen receptor pathway inhibitor (ARPI – abiraterone, enzalutamide, darolutamide) or both to ADT significantly improves overall survival. Exhibit 1 shows the Level 1 studies which have changed the standard of care.[4-14] The National Comprehensive Cancer Network (NCCN) Guidelines now recommend either ADT plus an ARPI or ADT plus docetaxel and abiraterone or darolutamide as category 1 recommendations.[15]

In selecting which ARPI to use, only abiraterone and darolutamide have been studied in the triple combination so are the recommended choices when ADT/ARPI/docetaxel is chosen. In choosing between abiraterone, apalutamide, and enzalutamide for use

Exhibit 1: Level 1 Evidence for Improved Overall Survival in mHSPC[4-14]

Studies	Intervention	Control	Comments
STAMPEDE-H	Prostate radiation + ADT (+/- docetaxel)	ADT (+/- docetaxel)	Benefit in low-volume disease subgroup
GETUG-15 CHAARTED STAMPEDE-C	Docetaxel + ADT	ADT	Benefit in high-volume subgroup
LATITUDE STAMPEDE-G	Abiraterone + ADT	ADT	Similar benefits by risk group
ARCHES ENZAMET	Enzalutamide + ADT	ADT	Similar benefits by risk group
TITAN	Apalutamide + ADT	ADT	Similar benefits by risk group
ARASENS	Darolutamide + ADT + docetaxel	ADT + docetaxel	Similar benefits for recurrent and de novo metastatic disease
PEACE-1	Abiraterone +ADT + docetaxel (+/- prostate radiation)	ADT + docetaxel (+/- prostate radiation)	Subgroup analysis

in combination with ADT alone, many clinicians find that enzalutamide is better tolerated and some study data supports lower rates of adverse events with this agent. The choice of therapy is between ADT/ARPI or ADT/ARPI/docetaxel. Clinicians in concert with the patient will have to make a decision between these regimens. Early studies using docetaxel showed the most benefit in those with a high volume of disease but more recent studies are showing benefits even in low-volume disease. Patients may prefer an all-oral regimen rather than having to endure chemotherapy.

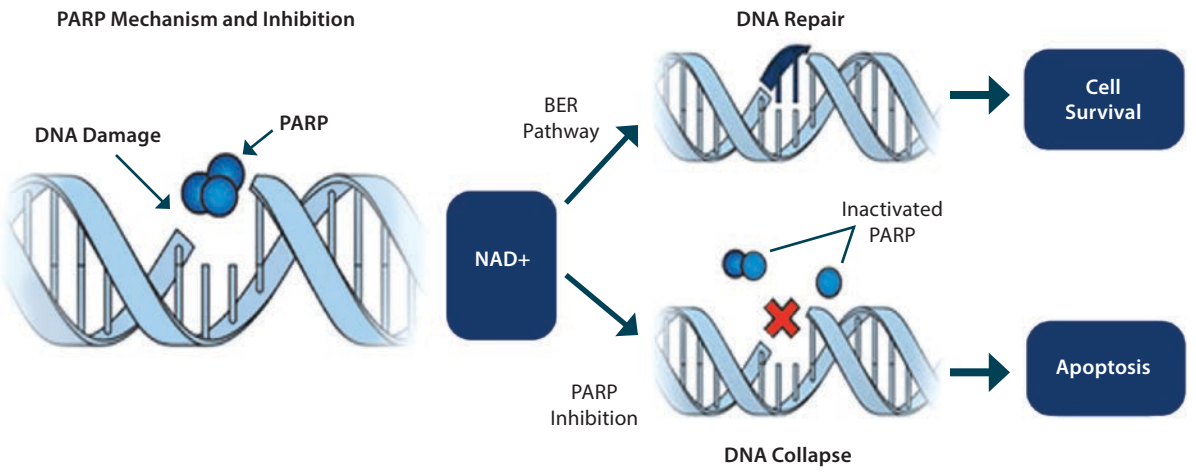
Eventually metastatic prostate cancer becomes resistant to androgen blocking agents. Castrate resistant prostate cancer (CRPC) is defined by disease progression despite ADT and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases. The treatment options for CRPC are numerous and depend on what prior therapy the patient has received, sites of disease, and molecular alterations. Two advances in CRPC treatment are the availability of poly-ADP ribose polymerase (PARP) inhibitors and lutetium Lu 177 vipivotide tetraxetan.

About 12 percent of patients with prostate cancer have germline DNA repair deficiencies caused by genetic mutations.[16] BRCA 2, BRCA 1, and ataxia-telangiectasia mutated (ATM) are the most common mutations. These mutations result in defective homologous DNA repair and transcription and cell cycle checkpoint regulation. PARP is one of the ways cells repair DNA when homologous repair deficiency exists; inhibition of PARP eliminates that avenue and cells die (Exhibit 2).

The first PARP inhibitor evaluated in CRPC was olaparib. It results in improved progression-free survival (PFS) in those with germline and somatic DNA repair genetic mutations.[17] The biggest benefit with olaparib is in those with BRCA mutation but the NCCN Guidelines recommend it for men with any DNA homologous repair mutation.[15] Other PARP inhibitors are options in the NCCN Guidelines but only olaparib has a Category 1 recommendation when used alone.[15]

PARP inhibitors have been studied in combination with ARPI. There are some data to suggest that a PARP inhibitor in combination with an ARPI in CRPC provides benefit even when DNA repair mutations are not present. The PARP inhibitor increases activity of the ARPI by androgen receptor dependent transcription, additionally, the ARPI induces homologous repair deficiency which increases PARP inhibitor activity.[18] Reports from combination trials show improved PFS and reduced risk of death. Final overall survival data have not yet been published.[19-21] Talazoparib/enzalutamide, niraparib/abiraterone, and olaparib/abiraterone are FDA-

Exhibit 2: Mechanism of Action of PARP Inhibitors



BER = base extension repair
NAD = nicotinamide adenine dinucleotide

approved combinations for CRPC in patients with HRR mutations and BRCA mutation, (respectively for second two). All three combinations are Category 1 recommendations in the NCCN Guidelines for patients with CRPC with no prior docetaxel or ARPI treatment.[15] Multiple clinical trials are testing PARP inhibitors in combination with other agents and in the hormone-sensitive setting.

There is a new imaging technique for prostate cancer – prostate-specific membrane antigen-positron emission tomography (PSMA-PET). PSMA is a well-established, prostate tissue-restricted, cell membrane target. PSMA can be overexpressed in metastatic prostate cancer relative to normal tissue and is present in more than 80 percent of men with metastatic disease.[22] Because of the increased sensitivity and specificity of PSMA-PET for detecting micro-metastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the NCCN Guidelines do not recommend that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not a more effective, front-line imaging tool for patients.[15] PSMA imaging is going to find many more metastatic cases than conventional imaging but whether earlier therapeutic intervention is beneficial is not yet known.

Lutetium Lu 177 vipivotide tetraxetan, a radiopharmaceutical, is the newest therapy for mCRPC. The active moiety, the radionuclide lutetium-177, is linked to a moiety that binds to PSMA. Upon binding to PSMA expressing cells, beta emission from lutetium-177 delivers radiation to the cells, as well as to surrounding cells, and induces DNA damage which leads to cell death. Lutetium Lu 177 vipivotide tetraxetan plus standard care compared to standard care significantly prolonged both imaging-based progression-free survival (median, 8.7 versus 3.4 months; $p < 0.001$) and overall survival (15.3 versus 11.3 months; $p < 0.001$).[23] The NCCN Guidelines list this therapy as a Category 1 treatment option for PSMA-positive mCRPC with prior docetaxel and ARPI treatment.[15] Ongoing studies are evaluating the role of this and other PSMA radioligands in earlier disease states.

Conclusion

ADT alone is no longer a standard of care for most patients with mHSPC because treatment intensification improves overall survival. All patients with mHSPC should receive an ARPI and possibly docetaxel in conjunction with ADT. PARP inhibitors have demonstrated efficacy in mCRPC and may be used in combination with ARPI. Lutetium Lu 177 vipivotide tetraxetan improves progression-free and overall survival in patients with PSMA PET-positive mCRPC with disease progression despite prior ARPI and chemotherapy.

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Innovative Approaches in the Management of Advanced Renal Cell Carcinoma: Managed Care Considerations on Targeted Therapy and Immunotherapy Combinations

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Summary

Substantial evolution in the treatment of metastatic renal cell carcinoma (RCC) has occurred in recent years with notable changes in the first-line setting. Doublet combination therapy with either two immune checkpoint inhibitors or a combination of an immune checkpoint and tyrosine kinase inhibitor is considered the standard of care. These regimens have led to a significant improvement in clinical outcomes and disease prognosis.

Key Points

- Choice of the most efficacious first-line therapy is very important given the high attrition rate from first and subsequent lines of therapies.
- The first-line therapeutic landscape has rapidly evolved with approval of multiple novel combinations.
- Choice of therapy is guided by many factors.
- With a multitude of possible therapeutic sequences, a definitive therapeutic sequence is unlikely.
- Clinical trials should be offered for every line since cure is unlikely with current therapy.

THERE ARE EIGHT KNOWN TYPES OF renal cell carcinoma (RCC) but most cases (75%) are clear-cell RCC which is the focus of this article. Unlike most cancers, the majority of RCC cases are diagnosed when the disease is still localized to the kidney (56%), but only 16 percent of cases are metastatic at diagnosis.[1] Surgical resection often cures RCC if it is diagnosed and treated when still localized to the kidney and the immediately surrounding tissue. With surgical treatment about 60 percent of patients are cured and 40 percent progress to eventually develop metastatic disease.

A range of factors predict poor survival with metastatic RCC (mRCC). The International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) prognostic model is used in patient selection for various therapies.[2] The factors included are performance status, time-to-therapy interval, and presence of anemia, hypercalcemia, neutrophilia, or thrombocytosis. Patients who do not have any of these risk factors belong to the favorable-risk category, patients with one or two are intermediate-risk category, and those with three or more belong to poor-risk category. In a study involving more than 1,000 patients in the IMDC consortium, median survival was 43 months in in the favorable-risk group, 22 months in the intermediate-risk, and eight months in the poor-risk category.[2]

In a study of real-world patients, conducted by the IMDC consortium, half of the patients were only

Exhibit 1: NCCN First-Line Treatment Selection in Advanced Clear Cell RCC[5]

Risk	Preferred Regimens
Favorable	• Axitinib + pembrolizumab (category 1)
	• Cabozantinib + nivolumab (category 1)
	• Lenvatinib + pembrolizumab (category 1)
Poor / Intermediate	• Axitinib + pembrolizumab (category 1)
	• Cabozantinib + nivolumab (category 1)
	• Nivolumab + ipilimumab (category 1)
	• Lenvatinib + pembrolizumab (category 1)
	• Cabozantinib

able to receive first-line therapy.[3] For the 50 percent who make it to second-line therapy, only 25 percent of those are able to receive a third-line. Hence, the selection of the most optimal therapy at a given time point is extremely important as many of these patients, especially those in the intermediate- and poor-risk category, may not survive to receive the subsequent lines of therapy.

The treatment of mRCC has evolved dramatically since the early 2000s. The ASCO Guidelines, updated in 2022, recommend first-line cytoreductive nephrectomy for select patients with kidney-in-place and favorable- or intermediate-risk disease.[4] For those who have already had a nephrectomy, an initial period of active surveillance may be offered if they are asymptomatic with a low burden of disease. Patients with favorable-risk disease who need systemic therapy may be offered an immune checkpoint inhibitor (ICI) in combination with a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI). Patients with intermediate- or poor-risk disease should be offered a doublet regimen (no recommendation was provided between ICIs or an ICI in combination with a VEGFR TKI). For select patients, monotherapy with either an ICI or a VEGFR TKI may be offered based on individual comorbidities. The National Comprehensive Cancer Network (NCCN) Guidelines provide similar recommendations (Exhibit 1).[5]

All the preferred regimen combinations in the NCCN Guidelines are superior to the historical standard of TKI monotherapy in improving overall survival (OS). However, no prospective studies directly compare the various combinations. The current practice of choosing one regimen over another is driven primarily by physician discretion and patient preference.[6] Factors that are considered in selecting first- or later-line therapy include IMDC-risk category, strength of clinical evidence, sarcomatoid differentiation, regimen toxicity profile, patient performance status, intolerance or lack of affordability of oral medications, cardiovascular comorbidities, history of autoimmune disease, anticipated patient adherence, and availability of a clinical trial.[6] Despite therapeutic advances, 5 percent to 20 percent of patients will have primary-progressive disease as their best overall response to first-line therapy.[6]

Numerous trials are ongoing investigating various combinations to better improve outcomes with first-line treatment, especially in those with intermediate- or poor-risk disease. In a trial published of dual immunotherapy (nivolumab/ipilimumab) and VEGFR TKI (cabozantinib) in the intermediate- or poor-risk mRCC setting, the triple-agent regimen resulted in significantly longer progression-free survival (PFS) than treatment with nivolumab/ipilimumab alone.[7] The improved PFS was at the expense of higher rates of Grade 3 and 4 adverse events in the triple therapy group (79% versus 59%). Final survival outcomes are not yet available from this trial and the NCCN Guidelines do not currently include this regimen. The future is likely to bring triple-agent regimens if one can be found which does not increase toxicity.

Second-line and later therapy is less well defined than first-line. Choice of a regimen will depend on whether immunotherapy was used in the first-line (Exhibit 2). It should be noted that there are no preferred regimens in the NCCN Guidelines.[5]

Exhibit 2: NCCN Second-Line and Later Options for Advanced Clear Cell RCC[5]

Immunotherapy History	Preferred Regimens	Other Recommended Regimens
• Naïve	• None	• Axitinib + pembrolizumab
		• Cabozantinib
		• Cabozantinib + nivolumab
		• Ipilimumab + nivolumab
		• Lenvatinib + pembrolizumab
		• Lenvatinib + everolimus
		• Nivolumab
• Prior	• None	• Axitinib
		• Cabozantinib
		• Lenvatinib + everolimus
		• Tivozanib

Clinical trials should be considered as an option for any line of mRCC treatment because no regimens have been shown to cure the disease once metastatic.

Additional immunotherapies, VEGFR TKIs, and new classes are all under investigation. Belzutifan is a hypoxia-inducible factor inhibitor which is being studied in combination with pembrolizumab and lenvatinib for advanced clear-cell RCC. It was approved by the FDA in 2021 for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated RCC, central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. VHL disease is a rare genetic condition that causes recurrent cyst and tumor growth.[8] As many as 70 percent of people with VHL disease develop clear-cell RCC by age 60 and RCC is a leading cause of death in patients with this manifestation of VHL disease. Epacadostat, an indoleamine 2,3-dioxygenase-1 (IDO1) inhibitor, is also in trials with pembrolizumab. IDO1 is strongly induced in inflammatory tissues by interferon-gamma and thereby contributes to the counter-regulatory effects of this cytokine on the immune response and the shaping of protumoral inflammation.[9] Numerous predictive biomarkers to guide the best initial choice of therapy and to optimize the sequential use of available therapeutic agents are also under investigation.

Conclusion

Choice of the most efficacious therapy for initial treatment of metastatic disease is very important given the high attrition rate from first to subsequent lines of therapies. The first-line therapeutic landscape has rapidly evolved with approval of multiple novel combinations. First- and second-line therapy is guided by strength of evidence, toxicity profile, comorbidities, patient and physician preference and financial concerns. With a multitude of possible therapeutic sequences, a definitive sequence of therapies is unlikely. Clinical trials should be offered for every line since cure is unlikely with current therapy.

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Uncovering Evidence-Based Treatment and Management of Psoriatic Arthritis: Examining Personalized Treatment Options

Arthur Kavanaugh, MD

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Summary

Psoriatic arthritis (PsA) is a complex heterogenous autoimmune disease that can be effectively treated with numerous agents which target the underlying pathology. Selection of a treatment in an individual patient depends on many factors. Research is ongoing to improve treatment selection based on both clinical and cellular phenotypes.

Key Points

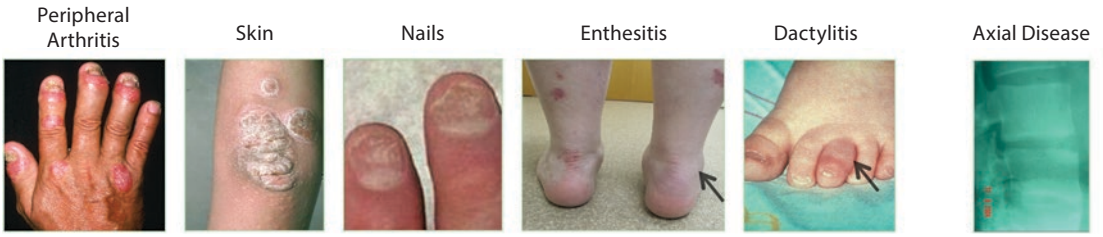
- Choice of PsA treatment is being tailored based on a patient's exposure to prior therapies, disease severity, comorbidities, individual manifestations of disease, medication toxicities, patient input, and costs.
- The challenge is selecting which agent is best for a given patient.
- Therapy is not yet personalized to a cellular phenotype.

PSORIATIC ARTHRITIS (PSA) IS A CHRONIC inflammatory arthritis associated with psoriasis. Approximately 25 percent of people with psoriasis will develop PsA with skin disease preceding arthritis, often by 10 years, in about 80 percent of patients. PsA clinical features include skin and nail psoriasis, peripheral arthritis, axial arthritis, enthesitis, and dactylitis (Exhibit 1).[1,2] Less common features are inflammatory bowel disease and iritis. In addition to causing an amount of pain, PsA can be disfiguring and disabling.[2] The ultimate expression of the disease varies widely among patients. For example, although all patients with PsA have peripheral arthritis only 25 percent gave dactylitis. As with other chronic inflammatory diseases, PsA is associated with accelerated cardiovascular disease and metabolic syndrome. Disease control reduces the impact of these comorbidities, joint damage from arthritis, and disability.

Although it is not completely known what initiates the PsA disease process, various components including genetics (epigenome), microbiome, and expression of proteins (proteome), are thought to play a role. Advances in understanding the immunopathogenesis of PsA has led to the development of agents targeting specific components of the dysregulated inflammatory and immune responses relevant to PsA including tumor necrosis factor (TNF) and various interleukins (IL-12, IL-17, IL-23).[3] The various available agents have shown differential responses across the various disease domains of PsA counter to what might have been expected. Also counter to what would be expected, a given class of agents does not work in all diseases mediated by the immune system (Exhibit 2).[3] For example, agents which target IL-6R are effective for rheumatoid arthritis but not PsA. Agents that target IL-17 are effective for PsA but can worsen inflammatory bowel disease.

In years past there were limited treatment options for PsA. It was treated like rheumatoid arthritis but this disease is very different from other forms of autoimmune arthritis. With numerous therapeutic choices, much more can now be done to manage

Exhibit 1: Clinical Features of Psoriatic Arthritis[1,2]



- Enthesitis: 30%
- Dactylitis: 25%
- Spondyloarthritis: 7% to 32%
- Nail Psoriasis: 60%
- Uveitis: 3.2%
- Inflammatory Bowel Disease: 3.3%

Exhibit 2: Disease Taxonomy via Specific Targeting[3]

	Cytokine targets						Non-cytokine targets				
Chronic Inflammatory Disease	**TNF**	**IL-6R**	**IL-1**	**IL-12/ IL-23**	**IL-17A**	**IL-23**	**Integrin**	**JAKS**	**CD-80/ CD-86**	**PDE4**	**CD20**
Rheumatoid arthritis	✓	✓	✓	–	–	–	–	✓	✓	–	✓
Autoinflammatory disease/sJIA	✓	✓	✓								
Crohn's disease	✓			✓	–	+	✓ Anti-α4, α4/β7	+			
Ulcerative colitis	✓			+	–	+	✓ Anti-α4/β7	✓		+	
Psoriasis	✓			✓	✓	✓	✓ Anti-LFA1 (CD11a)	+		✓	
Psoriatic arthritis	✓	+		✓	✓	+	+ Anti-LFA3	✓	✓	✓	–
Ankylosing spondylitis/axSpA	✓	–	–	–	✓	–		+		–	–
Multiple sclerosis	–						✓ Anti-α4				+

✓ FDA-approved
\+ Preliminary data on clinical efficacy
Insufficient data/not studied
– Disease-aggravating effect
– Failed to meet primary endpoints

Exhibit 3: Treatment Options

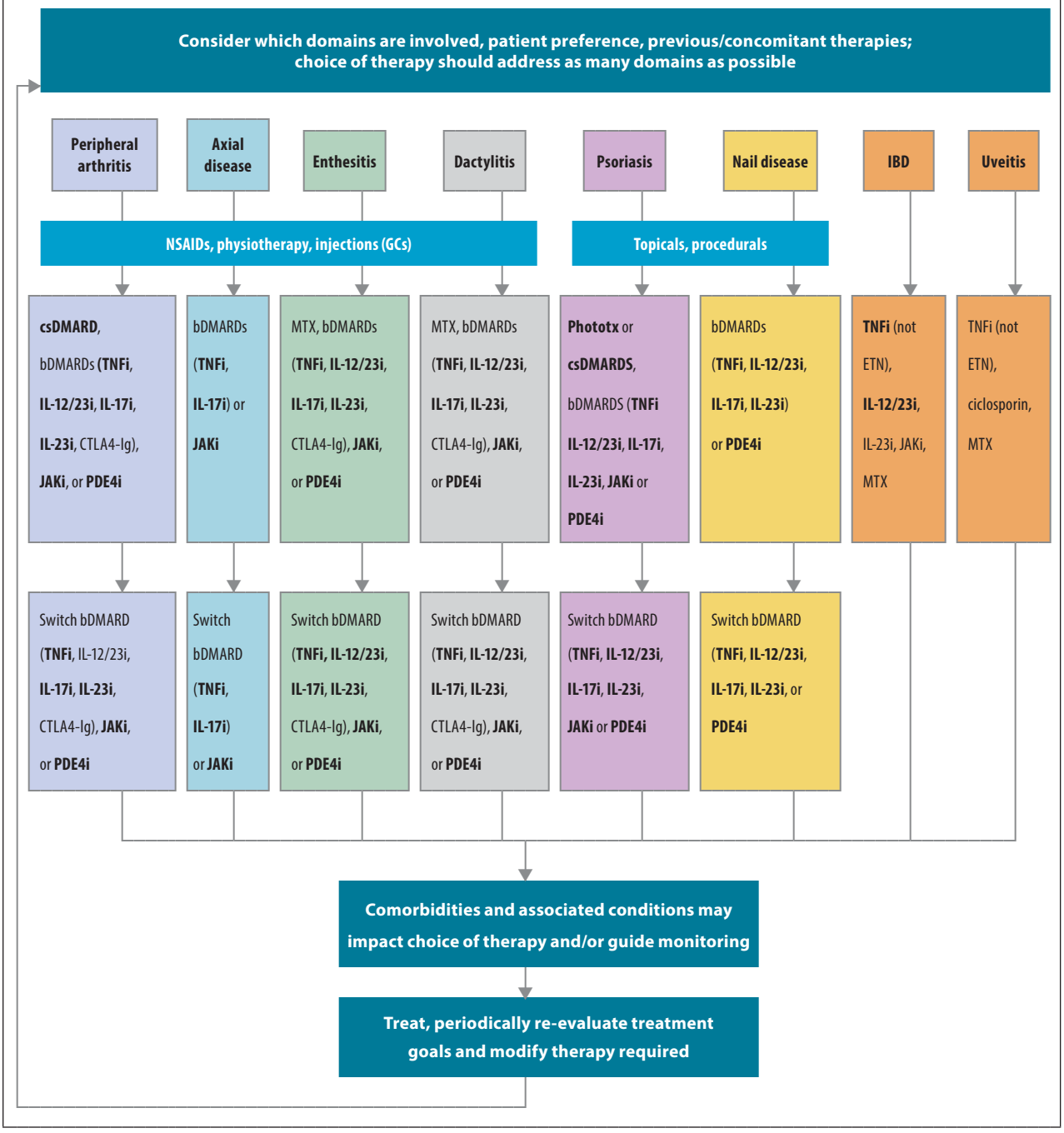
• **Adjunctive**
– NSAID/COX-2, steroids, analgesics, physical therapy
– Topicals to manage psoriasis
• **DMARDs**
– Methotrexate, leflunomide, cyclosporin, sulfasalazine
• **Biologics**
– TNF-Inhibitors (etanercept, infliximab, adalimumab, certolizumab, golimumab)
– Anti-IL-12/23 (ustekinumab)
– Anti-IL-17A (secukinumab, ixekizumab)
– Anti-IL-23 (guselkumab; risankizumab)
– CTLA-4-Ig (abatacept)
• **Jakinibs**
– Tofacitinib
– Upadacitinib
– Deucravacitinib
• **PDE4 inhibitor**
– Apremilast

TNF = tumor necrosis factor; IL = interleukin; CTLA-4-Ig = cytotoxic T lymphocyte associated antigen; PDE = phosphodiesterase

these patients. Unfortunately, there is no way to predict which patients will have poor outcomes from their disease, and thus need more aggressive therapy, or predict which patients will respond best to which medications. There are some data on which medications to choose based on which domain is most affected. There is much ongoing research in applying precision medicine to the PsA population.

Exhibit 3 shows the various treatment options for PsA. Many patients require pain management in addition to specific disease-modifying agents (DMARDs). The older less specific DMARD agents have some effect on skin manifestations and peripheral arthritis but do not improve axial arthritis and have questionable impact on other domains. Better efficacy results are obtained with the injectable biologics and the oral small molecule agents (JAK inhibitors, PDE4 inhibitor). The available comparative studies indicate that for arthritis, the TNF inhibitors and the anti-interleukin agents produce very similar outcomes.[4,5,6] A systematic review used Bayesian network meta-analysis to compare treatments on efficacy [American College of Rheumatology (ACR) response, Psoriasis Area and Severity Index (PASI) response, resolution of enthesitis and dactylitis] and safety (patients discontinuing due to adverse events) outcomes.[6] Despite similar efficacy for ACR response (measure of arthritis response), IL-17A and IL-17RA inhibitors and guselkumab offered preferential efficacy to TNF inhibitors in skin manifestations, and for enthesitis and dactylitis, thereby supporting drug selection based on predominant clinical phenotype. There are no comparative data for JAK inhibitors and apremilast to the injectable biologics but these are also treatment options especially for someone looking to avoid injections. The JAK inhibitors are effective across various PsA domains. Because of the long history of TNF inhibitor use and the availability of biosimilars in this class, this class continues to be the first-line choice for many rheumatologists. Other factors in choosing a treatment include a patient's exposure to prior therapies, disease severity, potential toxicity of a given therapy, comorbidities,

Exhibit 4: GRAPPA PsA Treatment Recommendations[7]



GRAPPA = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
DMARD = disease modifying antirheumatic drug; MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide; TNFi = tumor necrosis factor inhibitor; PDE-4i = phosphodiesterase 4 inhibitor; IL-12/23i = interleukin-12/23 inhibitor; SpA = spondyloarthritis; CS = corticosteroid; vit = vitamin; phototx = phototherapy; CSA = cyclosporin A.

and cost. It is also important for clinicians to identify what is important to the patient (i.e., what do they find most problematic about their disease) to target therapy. Exhibit 4 presents the most recent treatment algorithm for PsA.[7] The bolded choices in this algorithm have more data supporting their use for a given domain, however, it does not necessarily mean these agents are superior in terms of efficacy. The newest agent, deucravacitinib, a tyrosine kinase two (TYK2) inhibitor, is not yet included in the treatment guidelines.

For now, biologics and oral small molecule

inhibitors are used primarily as monotherapy in PsA treatment. There are some studies ongoing in other autoimmune diseases using combinations of biologics such as a TNF inhibitor and anti-IL-23 to target various parts of the immune system without producing excess immune system toxicities. Past studies of a combination of a TNF inhibitor and anti-IL-1 agent found more toxicity without additional clinical benefit.

Future developments in treating PsA will hopefully be improved prediction and prevention of PsA in those with psoriasis.[8] It will be interesting to see if earlier treatment of psoriasis with biologics will reduce the incidence of PsA. Methods for identifying and treating PsA earlier, before any joint damage, which would alter the disease course, should be forthcoming. There are also new treatment options on the horizon. This includes brepocitinib, another Jakinib, and more biologics targeting IL-17 and IL-23. Tildrakizumab and brodalumab are already FDA approved for psoriasis treatment and bimekizumab is currently being evaluated by the FDA for psoriasis. Precision medicine with targeted therapy based on cellular phenotypes will hopefully be in the future.

Conclusion

Currently, choice of PsA treatment is being tailored based on a patient's exposure to prior therapies, disease severity, comorbidities, individual manifestations of disease, medication toxicities, patient input, and costs. The challenge is still selecting the agent that is best for a given patient. Therapy is not yet personalized to the level of choosing an agent that will provide an optimum outcome.

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Patient-Focused Treatment Decisions in the Management of Ovarian Cancer: Managed Care Considerations in the Evolving Role of PARP Inhibitors

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Summary

Significant advances in the treatment of advanced ovarian cancer have been made over the last decade. One of these advances is the use of poly-ADP ribose polymerase (PARP) inhibitors. Although initially approved as later-line treatment, these agents are now used for maintenance therapy after a complete or partial response to first-line platinum-based chemotherapy.

Key Points

- Genetic testing is vital to identifying those who would benefit from PARP inhibitors.
- PARP inhibitors have significant efficacy in first-line maintenance setting.
- Maximizing tolerability and adherence with PARP inhibitors requires significant clinician effort.
- There is a challenge in optimizing cost management with this class of medication.

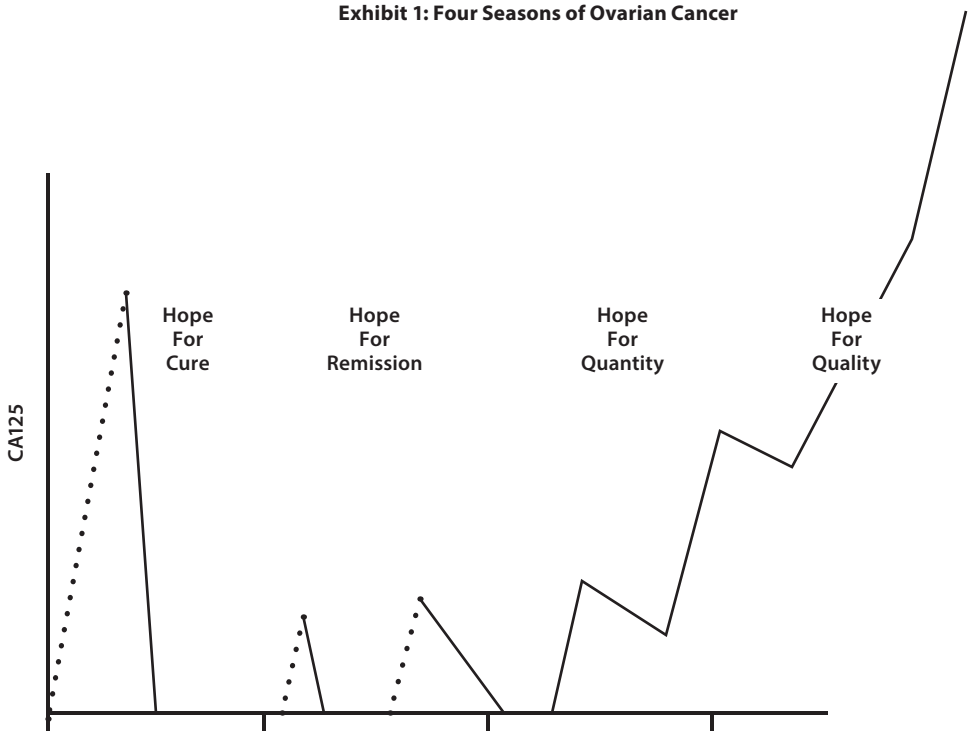
OVARIAN CANCER IS A CHALLENGING disease because most patients are not diagnosed before they already have advanced-stage disease and recurrence after treatment is common.[1] The experience of the patient with this disease can be mapped out by following the CA125 levels (Exhibit 1). Incidentally, CA125 was named as such because it was the one hundred and twenty-fifth in the line of markers when researchers were searching for a biomarker for this disease. CA125 is actually mucin-16 which increases as the tumor progresses. After surgery and radiation, levels decline and the patient hopes for a cure. Unfortunately, many patients have a relapse and then their hope is for remission. Chemotherapy is used for relapses to buy time for the patient.

Ovarian cancer is not one disease. The most common type is serous with 75 percent of cases being high-grade serous histology.[2] Endometrioid, clear cell, and mucinous are the other histological types. The other identifier of type is genetics. Breast cancer (BRCA) 1 and 2 mutated ovarian cancer is treated differently from cases without these mutations.

There have been multiple advances in the treatment of ovarian cancer since the late 1980s. Platinum-based chemotherapy (cisplatin, carboplatin), taxanes (paclitaxel), bevacizumab, immunotherapy, and PARP inhibitors have all come to market for various stages of the disease. The remaining focus here is the use of PARP inhibitors. Olaparib was first approved for ovarian cancer in 2014 and since then rucaparib and niraparib have been approved (Exhibit 2). Other PARP inhibitors (paroparib, talazoparib) are FDA-approved for other indications.

Ovarian cancer treatment strategy is based on three pillars – cytoreductive surgery, platinum-

Exhibit 1: Four Seasons of Ovarian Cancer

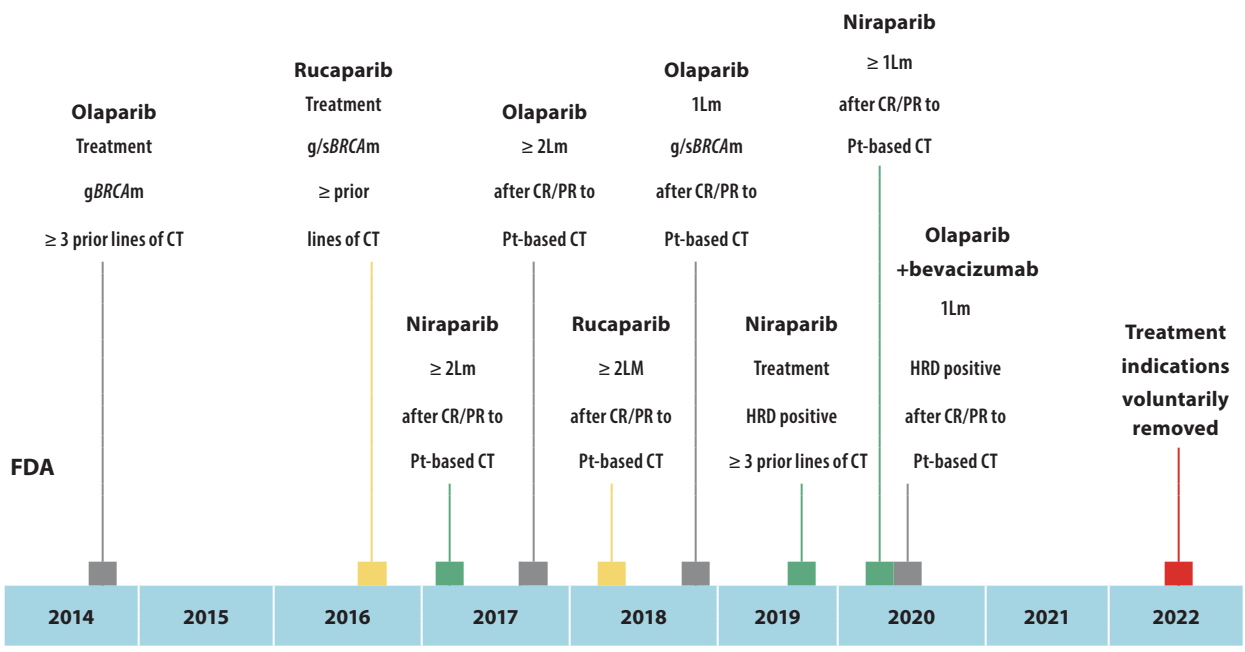


based chemotherapy, and targeted therapies. The latter in the last decade has provided a remarkable improvement in progression-free patients and, hopefully, in overall survival. Treatment is chosen based on histology, tumor genetic signature, remission duration, and number of prior lines of therapy. First-line treatment is surgery (primary or interval debulking) and primary or neoadjuvant chemotherapy with carboplatin and paclitaxel. After a complete or partial response to first-line platinum-based chemotherapy for Stages II to IV disease, patients will receive maintenance treatment with a PARP inhibitor until disease progression occurs. With disease progression another chemotherapy regimen will be tried. Whether it will be platinum-based will depend on the duration of remission. There are good data to say that cytotoxic treatment should be discontinued at disease progression after two consecutive lines of therapy. Only about 3 percent of patients will have benefit from a third line of chemotherapy.[3]

Exploiting the DNA damage response in BRCA 1 and 2 mutated tumors has led to advances in survival in those with these mutations. BRCA 1 and 2 are tumor suppressor genes which encode proteins that are involved in homologous repair (HR) of double-strand breaks in DNA. The HR pathway corrects the double-stranded DNA breaks using the homologous sequence in sister chromatid or on the second chromosome as a template. The process is efficient and restores the DNA to its pristine state. Failure of HR in those with germline or somatic BRCA mutations or other forms of HR deficiency (HRD) leads to the use of alternative nonhomologous end joining (NHEJ) pathways of DNA repair. NHEJ does not utilize a template as the DNA is simply trimmed and ligated, and this error-prone mechanism of repair can lead to genetic instability.[4] Accumulation of such mutagenic events is carcinogenic.

PARP plays a role in DNA repair through single-strand DNA break repair by NHEJ. Tumors defective in HR mechanisms may rely on PARP-mediated DNA repair for survival and are sensitive to its inhibition.[5] With PARP blockade by a PARP inhibitor, the single strand breaks are not repaired and are converted into double-stranded breaks with cell replication. The absence of functional BRCA and other HR repair mechanisms does not allow the repair of double-stranded breaks with consequent accumulation of fragmented DNA incompatible with cellular viability. This concept of coupling one dysfunctional DNA damage pathway with externally induced dysfunction in another is called synthetic lethality. Synthetic lethality is the basis of the use of PARP inhibitors in ovarian cancer with BRCA 1 and 2 mutations or HRD. Synthetic lethality also explains

Exhibit 2: PARP Inhibitor History



g/s*BRCA*m = germline/somatic *BRCA* mutation; CT = chemotherapy; Pt = platinum; CR = complete response; PR = partial response; HRD = homologous repair deficiency; Lm = line maintenance

the efficacy of platinum-based chemotherapy in this same population. PARP inhibitors may also increase tumor sensitivity to DNA-damaging agents such as chemotherapy.

Germline BRCA mutations occur in approximately 25 percent of patients with epithelial ovarian cancers while somatic BRCA mutations are estimated at 5 to 7 percent.[6] BRCA 1 and 2 mutations and other DNA damage response deficiencies are believed to affect up to 50 percent of high-grade epithelial ovarian cancer cases.[7]

All women diagnosed with ovarian cancer should have germline testing for BRCA1 and 2 plus other ovarian cancer susceptibility genes to steer treatment decisions. Disparities in both germline and somatic testing exist especially in women with Medicare or Medicaid insurance coverage or in women of color.[6,8] In one study (from 2011 to 2020), only 35.4 percent of women had germline testing.[8]

Olaparib maintenance after CR or PR response to first-line chemotherapy in BRCA mutation positive patients led to a 70 percent reduction in risk of progression and the benefits continued even after patients stop taking two years of maintenance.[9] There are also benefits to PARP inhibitor maintenance even in those who are HR-proficient. In a high risk for recurrence population, niraparib provided a clinically significant benefit in the HR-proficient subgroup with a 32 percent risk reduction in progression or death in addition to significant benefit in HRD subgroups.[10] There is more benefit with maintenance after first-line therapy rather than waiting to use a PARP inhibitor in later lines of therapy and the most benefit occurs in those with BRCA or HRD mutation. The National Comprehensive Cancer Network (NCCN) Guidelines recommend maintenance after first-line chemotherapy CR or PR. The choice of a PARP inhibitor will depend on whether bevacizumab was used during primary therapy and presence or absence of BRCA 1 or 2 mutation and HRD.[11]

Although the PARP inhibitors were previously used as treatment in second-line or later therapy, there appears to be a survival disadvantage in this setting. All three PARP inhibitors originally had an FDA-approved indication for treatment after two or more prior lines of therapy but these indications were voluntarily withdrawn in 2022 because of an approximately 30 percent increase in risk of death compared to chemotherapy.[12] The NCCN Guidelines now list PARP inhibitors as Category 3 for subsequent lines of therapy.[11] The Category 3 designation indicates based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Resistance to PARP inhibitors can occur through

BRCA reversion mutations.[13] BRCA reversion mutations also lead to platinum resistance. In one PARP inhibitor trial, these mutations were shown in 23 percent of patients with disease progression. PARP mutations are another source of resistance. Overcoming resistance is a major area of ongoing research.

Maximizing tolerability and adherence with PARP inhibitors requires significant clinician effort. Adverse events such as nausea, fatigue, hypertension, and headache can lead many patients to discontinue therapy. Successful maintenance therapy allows the patient to recover from chemotherapy before starting these agents. Monthly visits will also be required for laboratory testing. Clinicians need to educate patients on adverse events and provide them with management techniques. For example, for nausea, small frequent meals, good hydration, and gum or ginger can be helpful. Patients can also be given a prophylactic prescription for olanzapine – 2.5 mg every day.

There are also challenges in optimizing cost management with PARP inhibitors. The cost of these agents is $15,000 to $17,000 per month which is prohibitive for a patient unless they have prescription drug coverage. Because of the high cost of these agents and only a demonstrated impact on progression-free survival (PFS) so far, cost-effectiveness studies have not found them to be cost effective for maintenance therapy after response to first- or second-line chemotherapy.[14-16] In one trial, mean costs and progression-free quality adjusted life year (QALYs) were $827 and 3.4 months for observation, $46,157 and 5.7 for a BRCA mutation only maintenance, $109,368 and 8.5 for a germline BRCA and HRD-only strategy, and $169,127 and 8.8 for a maintenance for all strategy.[15] Maintenance in those with germline BRCA mutation had an incremental cost-effectiveness ratio of $243,092 per progression-free QALY compared with observation. Other strategies did not approach cost effectiveness. The authors of this study noted that treatment of patients with BRCA mutation alone or with HRD-positive tumors are preferred strategies compared with a maintenance for all strategy.[15]

Patients will need to make a choice of whether they wish to pursue maintenance and whether they are able to afford it. In a study measuring preferences of women with ovarian cancer regarding, risks, side events, costs and benefits afforded by maintenance therapy with a PARP inhibitor, participants valued overall survival (OS) and monthly costs most highly, followed by risk of death from MDS/AML (a rare adverse event), nausea, PFS, and fatigue.[17] Participants would accept 5 percent risk of MDS/AML if treatment provided 2.2 months additional OS or 4.8 months PFS. Participants would require gains of 2.6 months PFS to accept mild treatment-related fatigue and 4.4 months to accept mild nausea.

Conclusion

PARP inhibitors have significant efficacy in improving progression-free survival in first-line maintenance setting. Maximizing tolerability and adherence with PARP inhibitors requires significant clinician effort. There is a challenge in optimizing cost management with this class of medication.

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New Horizons in the Treatment and Management of Advanced Non-Small Cell Lung Cancer

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Summary

Treatment approaches for this disease when it is advanced have changed significantly over the past few years. These approaches, which target various cancer driving mutations and rev up the immune system to attack cancer cells, have led to improvement in progression-free and overall survival. Chemotherapy, particularly in combination with immunotherapy, still has a role in therapy.

Key Points

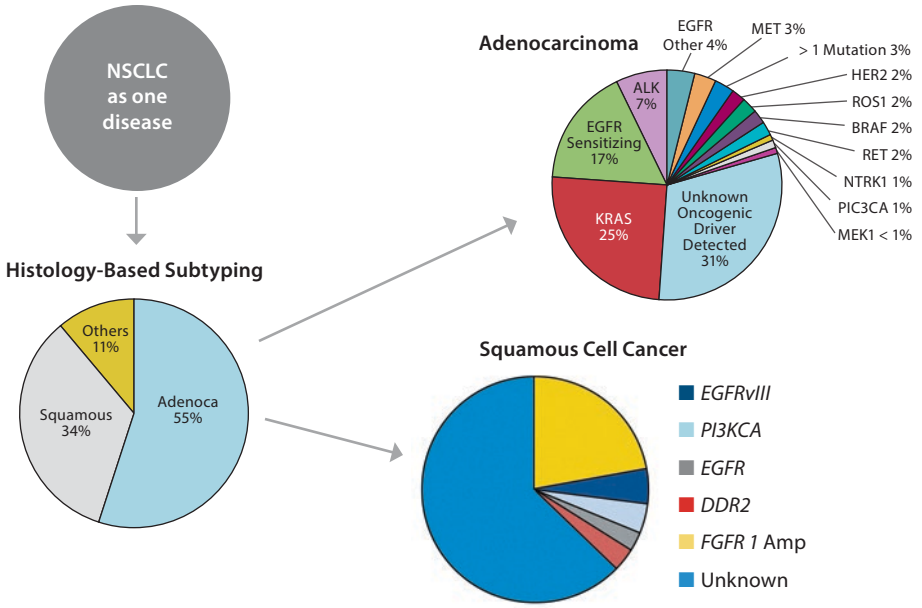
- Targeting driver mutations in this disease has improved survival.
- For those without driver mutations, immunotherapy agents are standard of care in most patients.
- Chemoimmunotherapy may be a more effective choice for many patients if they are able to tolerate it.

LUNG CANCER HAS MANY DIFFERENT subtypes which behave differently and impact treatment selection. Histology, presence of certain cell markers, and genetic mutations are used to distinguish the diverse types of lung cancer and select treatment. Non-small cell lung cancer (NSCLC) represents approximately 85 percent of all lung cancer cases and as shown in Exhibit 1, is not just one disease.[1,2] NSCLC is further subdivided into squamous (20% to 25% of NSCLC cases) and nonsquamous cell disease. Management of NSCLC which is advanced (Stage III or Stage IV) is where most of the advances in therapy have occurred.

Treatment of advanced NSCLC with various targeted therapies has exploded in the past 10 years. Exhibit 2 shows the various first- and second-line therapies by biomarker.[3] Broad molecular profiling and programmed death ligand one (PD-L1) testing to identify eligible patients are key components of patient care improvement.[3] Testing at presentation of advanced or metastatic disease is recommended, even if this testing was done at an earlier disease stage, as tumor cells change over time and in response to treatment.

Epidermal growth factor receptor (EGFR) mutations are found in 17 percent of cases in the United States.[1,2] They are more common in never or minimal smokers, younger patients, East Asian patients, and women. The majority are Exon 19 deletion or L858R mutation. Uncommon mutations include G719X, L861Q, S768I, and Exon 20 insertion. Although there are several agents FDA approved for Exon 19 del and L858R mutation, osimertinib is the first-line agent because of an improved adverse event profile and improved overall survival (OS) of almost seven months compared to other EGFR agents.[4] As with all EGFR targeting agents, resistance occurs to osimertinib. MET amplification, different EGFR

Exhibit 1: Non-small Cell Lung Cancer is Not One Disease[1,2]



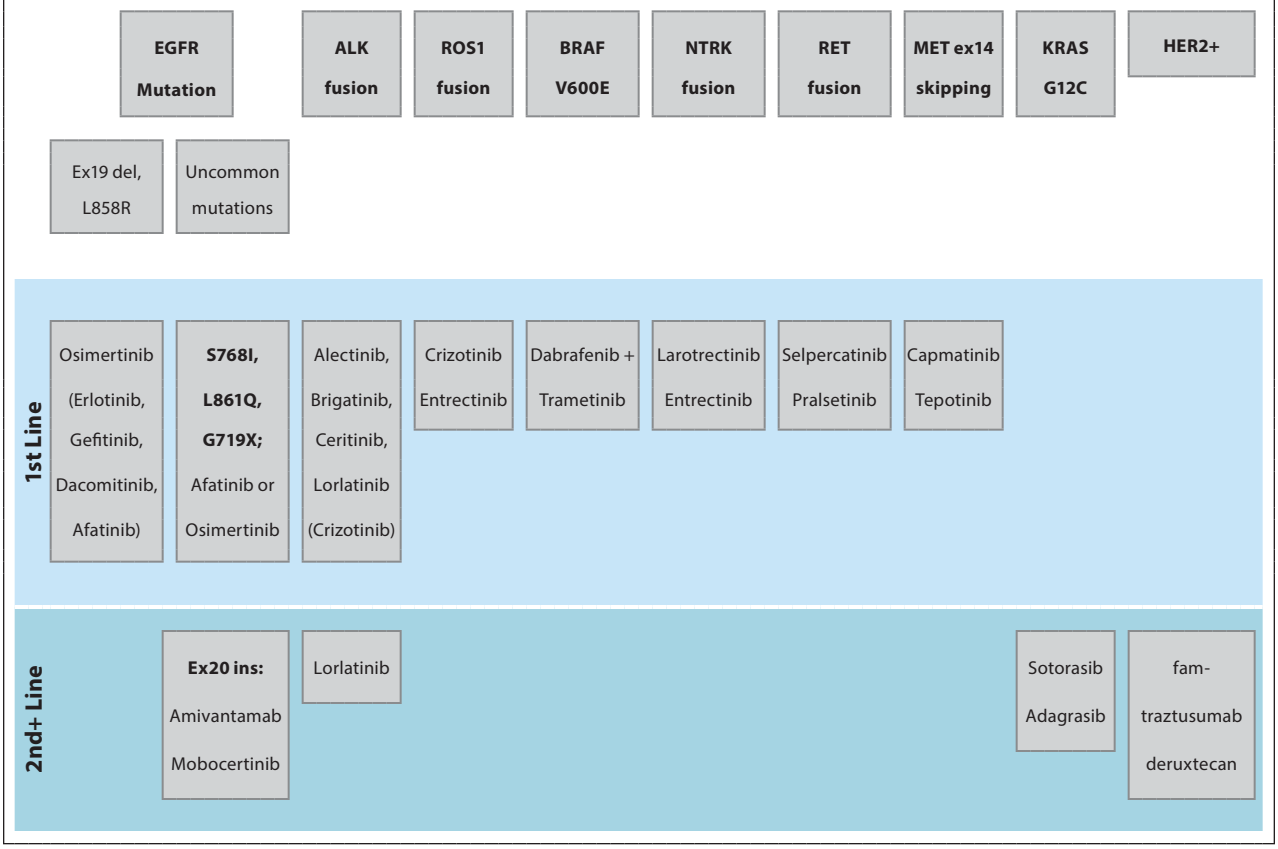
mutations, and transformation to small cell lung cancer can occur, thus molecular/genetic testing is recommended at disease progression after or during EGFR targeted therapy.[3] Osimertinib is also used as adjuvant therapy post-chemotherapy in high-risk Stage IB, Stage II and Stage III NSCLC with Exon 19 del or L858R mutation. Three years of osimertinib provided a disease-free survival (DFS) benefit and the four-year DFS rate was 70 percent (osimertinib) versus 29 percent (placebo).[5] This use may impact selection of therapy for metastatic disease. KRAS mutations occur in about 25 percent of adenocarcinoma NSCLC with G12C accounting for 12 percent of those. Sotorasib and adagrasib are both FDA approved for KRAS G12C mutated NSCLC as second-line treatment. The other known mutations in NSCLC occur in small percentages of cases but certain ones are targetable with FDA-approved agents as noted in Exhibit 2.

For patients who have no targetable biomarkers, immunotherapy with or without chemotherapy is the first-line treatment option. If PD-L1 expression is high [Tumor Proportion Score (TPS) ≥ 50%], single agent pembrolizumab, atezolizumab, or cemiplimab or chemoimmunotherapy (carboplatin doublet chemotherapy + pembrolizumab) are all Category 1 National Comprehensive Cancer Network recommendations.[3] For those with PD-L1, 1 percent to 49 percent, a carboplatin doublet and pembrolizumab are recommended. The agents included in the chemotherapy regimen depend on the histology of the tumor. Chemotherapy is the treatment option for those without targetable biomarkers or PD-L1 expression.

Choosing between single-agent immunotherapy or chemoimmunotherapy in those with high PD-L1 expression will depend on patient performance status, patient preference, and prior lines of treatment. Chemoimmunotherapy does cause a higher rate of adverse events, which patients may not be able to tolerate, but may provide a survival advantage. Researchers are trying to determine markers for identifying the patients who would most benefit from chemoimmunotherapy in the greater than 50 percent PD-L1 expression group. A meta-analysis of the available clinical trials found chemoimmunotherapy improved survival compared to immunotherapy alone in female patients, never smokers, those having a PD-L1 expression of 1 percent to 49 percent, or a low TMB and in patients with central nervous system metastasis.[6]

Additional agents are on the horizon. In May 2023, the FDA granted priority review to repotrectinib for the treatment of patients with ROS1-positive locally advanced or metastatic NSCLC. Repotrectinib inhibits diverse ROS1 fusions and resistance mutations including G2032R, is brain penetrant, and spares tropomyocin receptor kinase inhibition which limits certain adverse events. Additional non-gene-targeting therapies are also on the way.

Exhibit 2: Molecular Biomarker-Positive Advanced NSCLC[3]



Agents listed are preferred, those in ( ) are other options

Tusamitamab ravtansine is an antibody drug conjugate that binds to carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), which is highly expressed in about 25 percent of lung cancers. This agent recently moved into Phase III trials. Antibody drug conjugates could represent a new wave of treatments for advanced NSCLC.

Conclusion

NSCLC is a common and still highly fatal cancer for those with advanced disease, especially in older patients. Treatment approaches for this disease are evolving rapidly. Targeting driver mutations in this disease has improved survival. For those without driver mutations, immunotherapy agents are standard of care in most patients. Chemoimmunotherapy may be a more effective choice for many patients if they are able to tolerate it.

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Innovative Approaches in the Management of Overactive Bladder: Managed Care Strategies for Improved Clinical and Economic Outcomes

Matt T. Rosenberg, MD

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Summary

Overactive bladder (OAB) is a highly prevalent symptom condition that affects millions of men and women in the United Sates (U.S.). Not only can the symptoms of OAB be very bothersome, but OAB can have significant detrimental effects on many aspects of individuals' quality of life and productivity. Current treatments offer significant improvement of patient symptoms, patient quality of life and most patients can be identified and managed in the primary-care setting.

Key Points

- Diagnosis and treatment of OAB is within the realm of the primary-care setting
- Behavioral therapy, single use of anticholinergics or β3-agonists, and combination use of antimuscarinics or β3-agonists are effective treatment options.
- Additional interventions are available with specialist referral.

OVERACTIVE BLADDER (OAB) IS characterized by urinary urgency, usually accompanied by frequency and nocturia with or without urgency urinary incontinence, in the absence of a urinary tract infection or other pathology (Exhibit 1).[1,2] OAB symptoms occur due to failure of the bladder to store urine normally. It is important to note that lower urinary tract symptoms do not always indicate OAB. An enlarged prostate and several types of urinary incontinence can also cause similar symptoms.

It is estimated that 29.8 million adults aged 40 years and older in the U.S., have bothersome OAB symptoms.[3] The health burden of OAB is significant with 39 percent reporting interference with daily activities, 38 percent reporting decreased physical activity, and 34 percent reporting weight gain since OAB symptoms started.[4] Twelve percent of patients said OAB caused them to stay home, primarily due to incontinence fears. Those with OAB reported depression, anxiety, decreased self-esteem, negative effects on sexuality and relationships, and personal embarrassment.[4] To cope with symptoms of OAB, many patients employ elaborate behaviors to hide and manage urine loss.[5] These include wearing baggy dark clothes to hide wet spots, bathroom mapping, carrying extra clothes, and restricting fluid intake. OAB also affects work productivity and occupation. Those affected report two to three or more lost workdays due to medically-related absenteeism and decreased presenteeism than those without OAB.[4] There is also a higher rate of disability (14% versus 11%).

In addition to quality of life and work impact, OAB has significant economic costs. The projected cost in 2020 for the U.S., was $82.6 billion.[4] This is approximately $1,500 annually for those affected under 65 years of age and $6,500 for those aged 85

Exhibit 1:Defining OAB Symptoms[1,3]

Frequency	• Patient considers that he/she voids too often by day • Normal is < 8 times per 24 hours
Nocturia	• Waking to urinate during sleep hours • Considered a clinical problem if frequency is greater than twice a night
Urgency	• Sudden compelling desire to pass urine that is difficult to defer
Urgency urinary incontinence (UUI)	• Involuntary leakage accompanied by, or immediately preceded by, urgency

Exhibit 2: Diagnostic Workup[1,2]

Initial diagnostic process	• History • Physical exam • Urinalysis
Optional additional diagnostic measures	• Urine culture • Post voiding residual assessment • Bladder (voiding) diaries • Symptom questionnaire
Individualize	• Urodynamics, cystoscopy, and diagnostic renal and bladder ultrasound should not be used in the initial workup of uncomplicated patients

years and older. Urinary incontinence related to OAB is especially costly in terms of products such as adult diapers and caregiver assistance. Incontinence can be a major reason for nursing home care placement.

Diagnosis of OAB can be performed, the majority of the time, in the primary care provider office, where the providers should be asking about bladder/urinary symptoms at patient visits to identify bothersome OAB (Exhibit 2).[1,2] Only about 15 percent of patients with OAB are ever diagnosed and many patients don't discuss bladder issues with the provider unless prompted. A voiding diary is especially helpful to identify voiding frequency and voided volume and differentiates behavioral issues such as excessive fluid consumption and rushing urination from lower urinary tract pathology. A diary can alert the patient to habits and opportunities to modify behavior and can monitor treatment effects. For male patients, it can be more difficult to distinguish if symptoms are from OAB or benign prostatic hyperplasia which may require a referral to a urologist. Other indications for referral include history of recurrent urinary tract infections or other infections, prior pelvic irradiation, microscopic or gross hematuria, prior genitourinary surgery, elevated prostate-specific antigen, abnormal genital exam, suspicion of neurological cause of symptoms, meatal stenosis, history of genitourinary trauma, pelvic pain, and uncertain diagnosis.

First- and second-line treatment of OAB can be instituted in the primary care office (Exhibit 3).[1,2] Behavioral therapy is the first step and should be

Exhibit 3: Treatment Options[1,2]

First-line	• Behavioral therapies
Second-line	• Pharmacologic agents: - Beta-3 adrenergic or anticholinergics • Dose modification or change agent
Third-line	• Intra-detrusor onabotulinum toxin A • Peripheral tibial nerve stimulation (PTNS) • Sacral neuromodulation
Additional treatments	• Indwelling catheter • Augmentation cystoplasty or urinary diversion

offered to every patient. Components of behavioral therapy include bladder training, timed voiding, fluid and dietary management, pelvic floor exercises, biofeedback, and education. Behavioral therapy can be combined with medications for additional benefit. For second-line therapy, beta three (β3)-adrenergic receptor agonists (mirabegron, vibegron) or anticholinergics (fesoterodine, oxybutynin, solifenacin, tolterodine, trospium) are recommended. Anticholinergics reduce detrusor muscle contraction and sympathetic agonists stimulate relaxation. Four to six weeks of oral therapy is needed for efficacy to be evaluated. Dose modification or a switch to a different medication is recommended in the case of inadequate efficacy or poor tolerability. The choice of initial treatment will depend on factors such as prior anticholinergic use, past adverse events, patient preferences, comorbidities, other concomitant medications, cost, and insurance coverage and/or restrictions.

There are several issues with anticholinergic agents in the treatment of OAB. They primarily make symptoms better more than resolve all OAB symptoms. Adverse events are the major issues, and include dry mouth, constipation, and cognitive decline, especially in the elderly. A 2021 American Urogynecologic Society (AUGS) clinical consensus statement recommends that providers should counsel on the associated risk of cognitive impairment, dementia, and Alzheimer's disease associated with long-term anticholinergic medications.[7] This statement recommends avoiding use in women older than 70 years. The lowest effective dose should be prescribed and consideration should be given to changing or decreasing the dosage of other concomitant medications with anticholinergic properties to reduce anticholinergic load.[8]

Mirabegron and vibegron are once daily oral β3 agonists agents with no anticholinergic adverse events. These agents increase relaxation of the bladder muscles, rather than inhibit contraction, which makes excess urine retention less likely. Mirabegron is not recommended when a patient has severe uncontrolled hypertension but vibegron does not have this warning. Both agents have been shown to be safe and effective in those aged 65 years and older as well as younger patients.[9,10]

Combination with a low-dose antimuscarinic and mirabegron or vibegron in patients, who still have bothersome symptoms – especially incontinence, or who are on one class, is also an option because they have different mechanisms of action. The combination of 5 mg solifenacin with 50 mg mirabegron was superior to either alone in terms of number of micturitions per day, episodes of incontinence, and improvements in health-related quality of life.[11,12] Similar results were seen with the combination of vibegron and tolterodine.[13]

If behavioral therapy and medications do not adequately control symptoms or adverse events prevent adequate therapy, the patient should be referred to a specialist. Specialist-based interventions for OAB include intra-detrusor onabotulinum toxin A injections, peripheral tibial nerve stimulation (PTNS), and sacral neuromodulation. Options for when all else fails are indwelling catheter and augmentation cystoplasty or urinary diversion.

Conclusion

Overactive bladder doesn't take a patient's life – it

steals life from them. The untreated 85 percent of patients with OAB can be seen in the primary care physician office where it can be diagnosed efficiently by the primary care physician. The armamentarium of treatment options for primary care is extensive including behavioral therapy, single use of anticholinergics or β3-agonists, and combination use of antimuscarinics or β3-agonists. More extensive options are available for the specialist including sacral nerve stimulation, onabotulinumtoxin A, and percutaneous tibial nerve modulation.

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