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FEATURED ARTICLES INCLUDE:

Evolving Considerations in the Treatment and Management of HIV: Expert Strategies on Navigating ART Decisions for Optimized Clinical and Economic Outcomes

Adapting to Evolving Treatment Paradigms in Prostate Cancer: New Evidence and Opportunities

Best Practices in the Treatment and Management of Chronic Lymphocytic Leukemia: An In-Depth Look at BTK Inhibitors and Combination Regimens

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Evolving Considerations in the Treatment and Management of HIV: Expert Strategies on Navigating ART Decisions for Optimized Clinical and Economic Outcomes

Ian D. Frank, MD

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

Summary

Although effective treatments have turned HIV infection into a chronic manageable disease, those who are infected still require significant care and support to maintain therapy and deal with subsequent comorbidities. Prevention of infection in at risk patients is also an important strategy for dealing with the HIV epidemic in the United States (U.S.).

Key Points

- Aging with HIV infection is associated with an increased risk of common comorbidities.
- The currently recommended therapies are highly effective with low rates of treatment failure.
- Effective therapy reduces costs.
- Pre-Exposure Prophylaxis (PrEP) is an important intervention for HIV prevention in at risk people.

THE FIRST BASIC PRINCIPLE OF HUMAN immunodeficiency virus (HIV) treatment is that everyone with HIV should be treated. Patients are often started on therapy within a week of their diagnosis and treatment typically begins before all lab tests have returned. The goal of treatment is to reduce the HIV viral load to undetectable levels (< 50 copies/mL) as rapidly as possible and keep it there because people with undetectable viral loads do not suffer HIV-related infections and malignancies and do not transmit their infection to their sexual partners. This is the principle of *undetectable = untransmissible*.

Exhibit 1 shows all the currently available single-agent and combination antiretrovirals. Complete single-tablet regimens are one of the biggest evolutions in HIV treatment in the last few years and these significantly help with adherence and reduce patient burden. The complete single-tablet regimens are noted in the exhibit.

As different classes of antiretrovirals have been developed, the recommended regimens of antiretroviral therapy (ART) have changed with integrase inhibitors becoming a standard part of the recommended regimen due to superior efficacy and lower rates of adverse events compared to other classes. Exhibit 2 shows the recommended initial regimens in treatment naïve patients.[1,2] Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. Recommendations may differ based on baseline HIV levels, CD4+ cell count, other baseline testing, osteoporosis status, and pregnancy status or intent.

HIV has become a chronic manageable disease with effective therapy, however, as patients age, they accumulate a higher number of comorbidities than those patients without HIV. Prevalence and burden of non-AIDS-related comorbidities are high in people with, or at-risk for, HIV. This is

Exhibit 1: Antiretroviral Agents

Nucleoside reverse transcriptase inhibitors	Non-nucleoside reverse transcriptase inhibitors	Protease Inhibitors	Integrase Inhibitors	Attachment/Post-Attachment Inhibitors
Abacavir	Doravirine	Atazanavir	Bictegravir	Fostemsavir
Emtricitabine	Efavirenz	Darunavir	Dolutegravir	Ibalizumab
Lamivudine	Etravirine	Fosamprenavir	Elvitegravir	
Tenofovir (disoproxil fumarate, alafenamide)	Nevirapine	Lopinavir/ritonavir	Raltegravir	
Zidovudine	Rilpivirine	Saquinavir		
		Tipranavir		

C-C chemokine receptor type 5 Inhibitors	Fusion Inhibitors
Maraviroc	Enfuvirtide

Single Tablet Regimens

Abacavir/lamivudine
Abacavir/lamivudine/dolutegravir
Atazanavir/cobicistat
Bictegravir/emtricitabine/tenofovir AF
Darunavir/cobicistat
Darunavir/cobicistat/emtricitabine/tenofovir AF
Dolutegravir/lamivudine
Dolutegravir/rilpivirine
Doravirine/lamivudine/tenofovir DF
Efavirenz/emtricitabine/tenofovir DF
Efavirenz/lamivudine/tenofovir DF
Efavirenz/emtricitabine/tenofovir DF
Elvitegravir/cobicistat/emtricitabine/tenofovir AF
Rilpivirine/emtricitabine/tenofovir AF
Rilpivirine/emtricitabine/tenofovir DF
Tenofovir DF/emtricitabine
Tenofovir AF/emtricitabine
Tenofovir DF/lamivudine
Zidovudine/lamivudine

Red Text = complete regimen

Exhibit 2: Recommended Regimens for First-Line ART in Most Patients with HIV Infection[1,2]

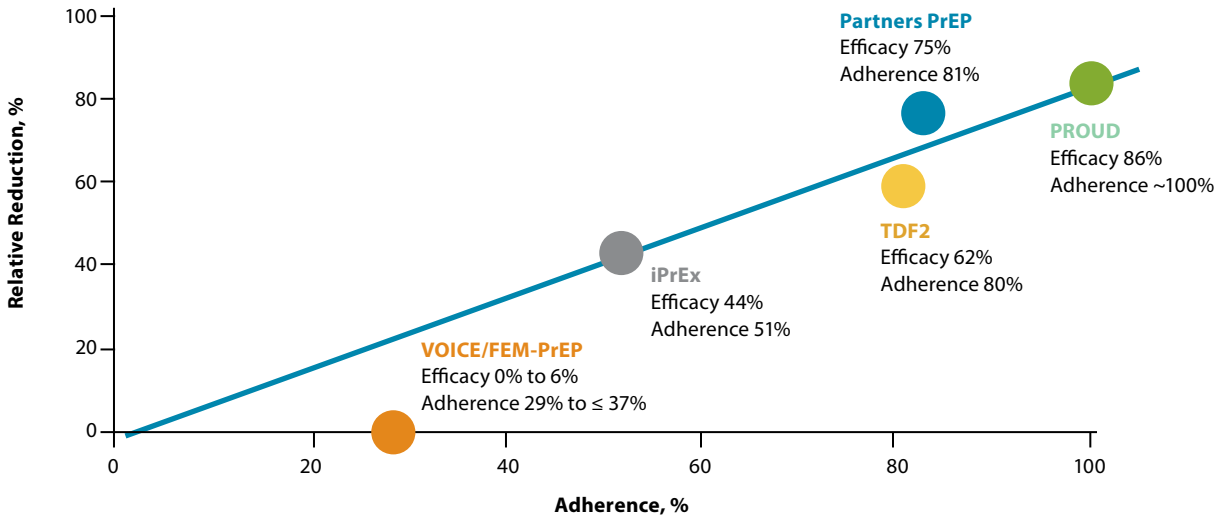
Class	Department of Health and Human Services	International Antiviral Society–USA Panel
INSTI	• Bictegravir/emtricitabine/TAF*	• Bictegravir/emtricitabine/TAF*
	• Dolutegravir/abacavir/lamivudine*	• Dolutegravir + TAF/FTC or TDF/FTC or TDF/3TC
	• DTG + (TAF or TDF) + (FTC or 3TC)	• DTG/3TC*^
	• DTG/3TC*^	

TAF= tenofovir AF; TDF= tenofovir DF; DTG = dolutegravir; FTC = emtricitabine; 3TC = lamivudine
* Single-tablet regimens
^Not recommended for patients with HIV RNA > 500,000 copies/mL, HBV co-infection, or prior to HIV genotypic resistance test availability

particularly true for hypertension, psychiatric illness, dyslipidemia, liver disease, and bone diseases. Various antiretrovirals can lead to some of these complications. For example, cardiovascular disease can be related to abacavir and most protease inhibitors; hyperlipidemia occurs with ritonavir, cobicistat, and efavirenz; hypertension, kidney disease, diabetes, and osteopenia/osteoporosis are other frequent antiretroviral-related complications.

Weight gain from antiretrovirals is another common complication and may contribute to the development of many other complications. In one study, patients gained up to 10 kg with dolutegravir/emtricitabine/tenofovir alafenamide and 5 kg with dolutegravir/emtricitabine/tenofovir disoproxil fumarate and efavirenz/emtricitabine/tenofovir disoproxil fumarate.[3] Integrase strand transfer inhibitor (INSTI)-based regimens are

Exhibit 3: Reduction in HIV Incidence Mirrors Medication Adherence[7-12]



associated with more rapid weight gain than non-INSTI regimens and are associated with insulin resistance.[4,5] Weight gained with any regimen is not easily lost with a switch to an alternative regimen.

Over time, there can be many reasons a patient requires a regimen switch even if they have achieved viral suppression. Convenience is one reason, and for patients on multiple separate medications daily, a switch to a single tablet regimen may be desired. Single-table regimens can be especially beneficial as noted previously in those with adherence issues. Development of a new comorbidity or starting a new non-HIV medication with drug interactions with a current HIV regimen are other reasons to make a switch. Pregnancy is a very common reason for a regimen change.

Before making a regimen switch, the clinician should 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 or a next-generation INSTI or boosted protease inhibitor with one additional active drug 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.

In addition to HIV treatment, prevention of infection is also important. Pre-Exposure Prophylaxis (PrEP) is an important intervention for HIV prevention. This intervention requires the taking of an antiretroviral medication if engaging in risk behavior to prevent HIV acquisition. Currently PrEP is recommended for men who have sex with other men, transgender people who have sex with men, 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. Two oral products approved for this use are single tablet daily regimens of emtricitabine and tenofovir alafenamide (Descovy®) or emtricitabine and tenofovir disoproxil fumarate (Truvada®). Both regimens are effective in preventing HIV infection and have been shown to cause low rates of adverse events.[6] Emtricitabine and tenofovir alafenamide has more favorable effects on bone mineral density and biomarkers of renal safety than emtricitabine and tenofovir disoproxil fumarate. Importantly, reduction in HIV incidence is only effective if the person is adherent with the regimen (Exhibit 3).[7-12] A new option which might improve adherence is long-acting injectable cabotegravir (Apretude®) 600 mg, given intramuscularly every eight weeks, which was FDA-approved in 2021 and was more effective than the oral regimens in two studies.[13,14]

All data indicate that everyone with HIV infection should be on antiretroviral therapy. Achieving a viral load < 200 copies/mL prevents ongoing transmission. Patients with viral loads < 200 copies/mL rarely get HIV-related complications that require hospitalization. Avoiding hospitalization and complications of therapy are major opportunities

Exhibit 4: Proprietary versus Generic Costs[15]

Combination	Pills per Day	WAC ($ per month)
Dolutegravir + emtricitabine/tenofovir AF or DF	2	$3,307 (TAF); $3,459 (TDF)
Dolutegravir + lamivudine/tenofovir DF (generic)	2	$2,922
Dolutegravir/lamivudine	1	$2,527
Dolutegravir + lamivudine (generic)	2	$1,992 - $2,260
Darunavir/cobicistat/emtricitabine/tenofovir AF	1	$4,065
Darunavir + ritonavir (generic) + lamivudine/tenofovir DF (generic)	3	$2,930
Efavirenz/emtricitabine/tenofovir DF	1	$2,995
Efavirenz/lamivudine/tenofovir DF (generic)	1	$1,634
Efavirenz/emtricitabine/tenofovir DF (generic)	1	$2,366
Emtricitabine/tenofovir DF	1	$1,842

to save 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 are critical for treatment success. Missing doses leads to resistance as well as loss of immunologic benefit.

The clinical benefits, public health impact, and cost-effectiveness of HIV treatment have been well established since the advent of combination ART and the expanded use of ART is one of the four pillars of the "Ending the HIV Epidemic: A Plan for America" initiative.[15] However, HIV treatment with ART is costly. The commonly used combination therapy regimens have a wholesale acquisition cost of approximately $3,000 or more per month. Some of these regimens now have generics available which provide some cost savings (Exhibit 4).[15] However, from a patient perspective, most patients with HIV do not pay for ART. Medical assistance and the Ryan White/AIDS Drug Assistance programs pay for ART for many. Copay cards issued by manufacturers make up the difference between costs covered by insurance or Ryan White Assistance program support. Overall, there is minimal incentive to use generics unless copays are eliminated.

Conclusion

People with HIV are living longer but aging with HIV infection is associated with an increased risk of common comorbidities. The currently recommended therapies are highly effective with low rates of treatment failure. Switching therapy may be necessary to simplify regimens and avoid toxicities and drug-on-drug interactions. New treatment strategies and new drugs continue to be developed. Importantly, effective therapy reduces costs, no matter which is used. Generics and less expensive combinations may be able to replace more expensive agents in some situations.

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Adapting to Evolving Treatment Paradigms in Prostate Cancer: New Evidence and Opportunities

Scott T. Tagawa, MD, MS, FACP

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

Summary

Translational therapy has led to clinically relevant improvements for patients with prostate cancer. The goal is to target the right patient with the right mechanism of therapy. A new imaging tool for identifying prostate specific metastases and a radiopharmaceutical for treating one subtype of metastatic disease are now available. The treatment of non-metastatic castrate-resistant disease is advancing.

Key Points

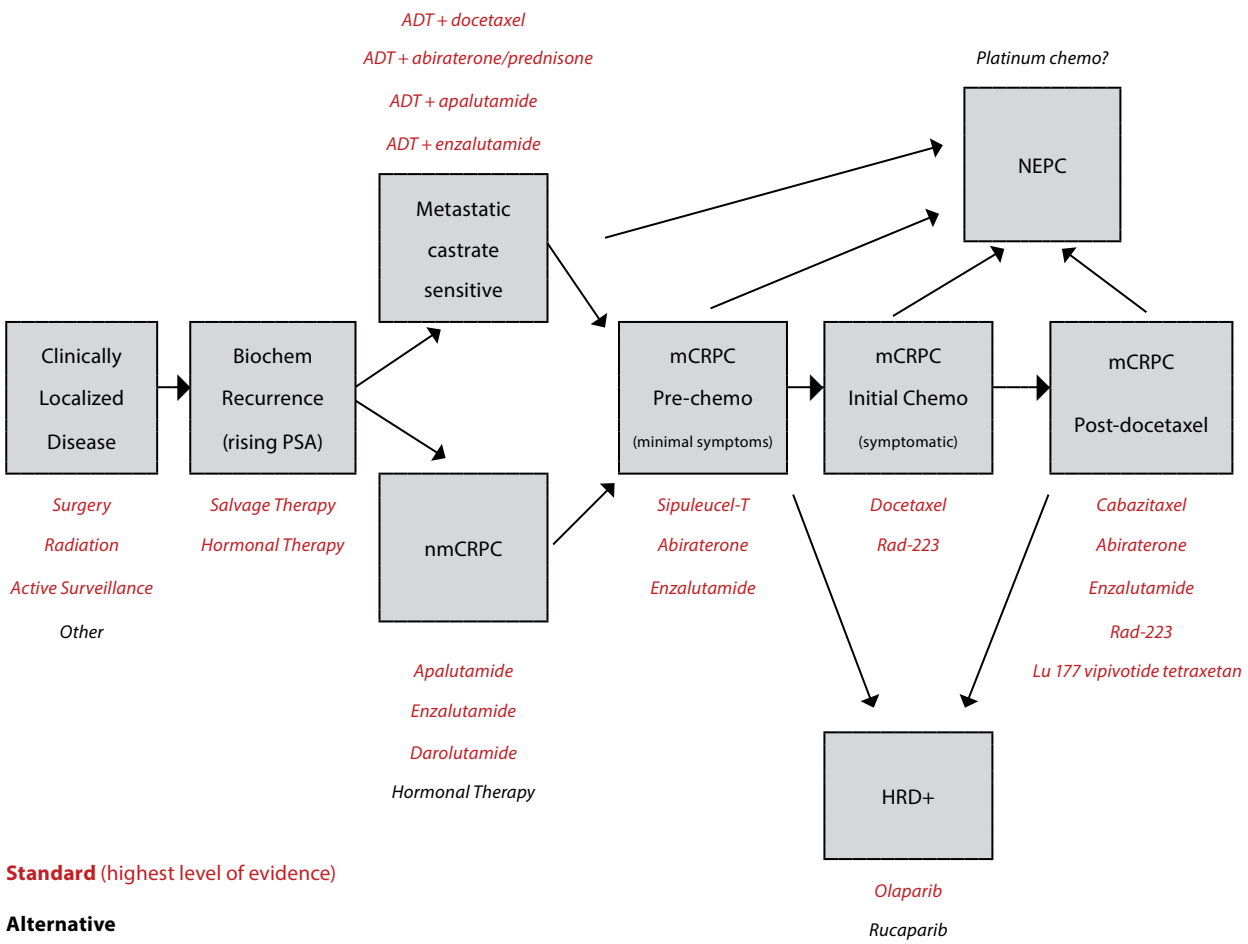
- Multiple therapies provide a survival benefit in metastatic castration-resistant prostate cancer (mCRPC).
- Prostate-specific membrane antigen (PSMA) imaging is going to find many more metastatic cases than conventional imaging.
- The modest benefit of potent androgen receptor (AR) pathway inhibition seen in mCRPC setting is magnified when these agents are used in nonmetastatic castration-resistant prostate cancer (nmCRPC).
- Prostate cancer treatment has finally entered the genomic precision medicine era, but no patient can benefit without PSMA or homologous repair deficiency testing.

PROSTATE CANCER INCLUDES SEVERAL disease states including locally advanced, biochemical recurrence, castrate sensitive, castrate-resistant metastatic disease, and neuroendocrine (Exhibit 1). Neuroendocrine prostate cancer (NEPC) is an aggressive variant of prostate cancer that may arise de novo or as a mechanism of resistance in patients previously treated with hormonal therapies for prostate adenocarcinoma. The various disease states are managed differently. The focus of the remainder of this article is on areas with recent advances in treating mCRPC and nmCRPC.

mCRPC is metastatic disease on imaging, testosterone ≤ 50 ng/dL (castrate level), and a rising prostate specific antigen (PSA) or new metastases on imaging. nmCRPC is where there is no evidence of metastatic disease on imaging and a castrate testosterone but a rising PSA. Chemotherapy with or without other agents has a role in managing castrate sensitive and resistant metastatic disease. Taxanes are the only class of chemotherapy with demonstrated survival benefits. Docetaxel is the usual first-line chemotherapy and cabazitaxel is typically used second-line after docetaxel but may be used first-line in patients more likely to have adverse events with docetaxel. Both have been shown to prolong survival. In addition to typical chemotherapy mechanisms, the taxanes have an inhibitory effect on androgen receptors, which drive prostate cancer and are the target of hormonal therapies.[1]

The newest agent for mCRPC is lutetium Lu 177 vipivotide tetraxetan (Pluvicto®) which was FDA-approved in February 2022. This is a radioligand therapeutic agent indicated for the treatment of adult patients with PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy. PSMA is the single most well-established, prostate-restricted, cell membrane target known.[2] It is validated in cells and in humans in clinic, is mostly prostate-restricted, and is a cell membrane target. PSMA can be overexpressed in metastatic prostate cancer relative to normal tissue

Exhibit 1: Prostate Cancer Disease States and Recommended Treatments



ADT = androgen deprivation therapy; CRPC = castrate-resistant prostate cancer; nmCRPC = nonmetastatic castrate-resistant prostate cancer; mCRPC = metastatic castrate-resistant prostate cancer; NEPC = neuroendocrine prostate cancer; HRD+ = homologous repair deficiency

and is present in > 80 percent of men with metastatic disease.[3,4] PSMA positive disease is demonstrated with a PSMA-PET scan, a next generation imaging technique. The active moiety – radionuclide lutetium-177 – is linked to a moiety that binds to PSMA, a transmembrane protein that is expressed in prostate cancer, including mCRPC. Upon binding to PSMA expressing cells, beta emission from lutetium-177 delivers radiation to PSMA-expressing cells, as well as to surrounding cells, and induces DNA damage which can lead to cell death.

The trial that led to FDA approval found that 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 (OS), (median, 15.3 versus 11.3 months; $p < 0.001$).[5] This therapy may replace second-line chemotherapy in PSMA positive patients. In a Phase II trial against cabazitaxel, in men with mCRPC, this therapy led to a better PSA response and fewer Grade 3 or 4 adverse events.[6] No comparative survival data are yet available. The National Comprehensive Cancer Network (NCCN) Guidelines list this therapy as category 1 for patients with prior docetaxel exposure, prior hormonal therapy, and are PSMA positive.[7]

About 12 percent of men with metastatic prostate cancer have DNA-repair mutations.[8] Those with a homologous recombination repair gene mutation (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L) who have been treated previously with AR-directed therapy should receive olaparib, a PARP inhibitor.[7] Olaparib improves OS in the mCRPC setting.[9] Combinations of PARP inhibitor and androgen deprivation therapy such as abiraterone plus olaparib are showing

interesting results in early phase studies and may be the treatment of choice in the future. Unfortunately, several studies have shown that many men with metastatic castration-sensitive disease are being treated inappropriately with androgen deprivation therapy alone rather than the recommended combinations (Exhibit 1). Fifty-six to 87 percent of patients are receiving inferior therapy.[10-12] Lack of treatment is also an issue. One study found that only 77 percent of patients with metastatic disease received at least one line of life-prolonging therapy.[12]

Another recent change in therapy is the treatment of nmCRPC. Three agents have been demonstrated to improve metastases-free survival and OS in nmCRPC – apalutamide, enzalutamide, and darolutamide.[13-15] These three agents are potent androgen-receptor antagonists and are all FDA-approved for nmCRPC. The patient population in the approval trials for these three agents had to have been treated earlier with androgen deprivation therapy and conventional imaging was used to demonstrate benefit. Increasing numbers of patients who were previously identified with nmCRPC will likely show metastatic disease on more sensitive advanced imaging with PSMA-PET.

There is compelling evidence that PSMA-PET has superior sensitivity and specificity to conventional imaging. In a retrospective study that included 200 patients classified as nmCRPC on conventional imaging, PSA > 2 ng/mL, and high-risk for metastatic disease (PSA doubling time of ≤ 10 months and/or Gleason score of ≥ 8) from six high-volume PET centers found PSMA-PET was positive in 196 of 200 patients.[16] Overall, 44 percent had pelvic diseases, including 24 percent with local prostate bed recurrence, and 55 percent had metastatic (M1) disease despite negative conventional imaging. Fifty-five percent actually had mCRPC instead of nmCRPC. Because of the increased sensitivity and specificity of PSMA-PET for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the NCCN Guidelines state that conventional imaging is not a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective, frontline imaging tool for these patients.[7]

Conclusion

Prostate cancer generally remains a hormone sensitive disease throughout its lifecycle but variants such as NEPC exist and need to be recognized. Multiple therapies provide a survival benefit in mCRPC. PSMA imaging is going to find many more metastatic cases than conventional imaging. The modest benefit of potent AR pathway inhibition seen in mCRPC setting is magnified when these agents are used in nmCRPC. Prostate cancer treatment has finally entered the genomic precision medicine era but no patient can benefit without testing PSMA or homologous repair deficiency testing.

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Best Practices in the Treatment and Management of Chronic Lymphocytic Leukemia: An In-Depth Look at BTK Inhibitors and Combination Regimens

John N. Allan, MD

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

Summary

The management of chronic lymphocytic leukemia has undergone unprecedented changes over the last decade. Modern targeted therapies have replaced chemotherapy in most cases. Because there are several targeted therapy options, patients can be treated with multiple lines of therapy when disease progression or intolerance occurs.

Key Points

- BTK inhibitors have demonstrated long-term efficacy and safety data.
- Later generation agents are replacing ibrutinib as preferred therapy because of better tolerance.
- Combination-venetoclax based approaches demonstrate high rates of undetectable minimal residual disease (uMRD) providing potential for time-limited therapy.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)/small cell lymphoma (SLL) is a neoplasm composed of monomorphic small mature B cells that co-express CD5 and CD23 and is the most frequent type of leukemia in adults.[1] CLL requires a greater than $5x10^9$/L clonal B-cell count. SLL is restricted to cases less than $5x10^9$/L cell count but with documented nodal, splenic, or extramedullary involvement and accounts for 15 percent of cases. For purposes of this article CLL and SLL are referred to as CLL.

CLL represents 1.2 percent of all cancers diagnosed annually in the United States (U.S.) and there are approximately 21,000 cases and 4,000 deaths annually from CLL in the U.S.[2] The five-year survival rate is 86.1 percent. Patients are classified as having favorable, intermediate, or unfavorable disease based on a range of factors. Those with favorable-risk disease have better survival than those with intermediate- or unfavorable-risk. Exhibit 1 shows the molecular factors which define risk with CLL.[3] Data from the real-world informCLL registry has shown that the majority of patients in the U.S. with CLL are managed by community-based oncologists and are less likely to have known prognostic factors measured, especially del(17p)/TP53 and IGHV mutational status and FISH testing.[4] The del(17p)/TP53 mutation is important because it is associated with poor response rates to chemoimmunotherapy (CIT). In addition to issues with prognostic marker testing, data from this registry indicate a 'knowledge gap' in terms of selection of therapies. Sixty-one percent of patients in the registry who received CIT received bendamustine and rituximab which has been shown to be inferior to all other options. Care of patients with CLL could be improved by referring all patients to a CLL specialist rather than a general oncologist.

CLL is an incurable disease with a heterogeneous clinical course, for which treatment decisions still rely on conventional parameters (such as clinical stage and lymphocyte doubling time).[1] Improvements in understanding the prognostic value of different genetic lesions, particularly those associated with chemoresistance, progression to highly aggressive forms of CLL, and the advent of new therapies targeting crucial biological pathways are all significant advances in clinical management.

Exhibit 1: Molecular Features that Define Risk in CLL[3]

Method of Detection	Prognostic Variable	Risk category
Interphase cytogenetics (FISH)	del(17p)	Unfavorable
	del(11q)	Unfavorable
	+12	Intermediate
	Normal	Intermediate
	del(13q) (as a sole abnormality)	Favorable
DNA sequencing	*TP53*	Wild-type: favorable Mutated: Unfavorable
	IGHV	> 2% mutation: Favorable ≤ 2% mutation: Unfavorable
CpG-stimulated metaphase karyotype	Complex karyotype (≥ 3 unrelated clonal chromosome abnormalities in more than one cell on karyotype)	Unfavorable

IGHV = immunoglobulin heavy chain gene

Exhibit 2: NCCN Recommended First-Line Regimens[3]

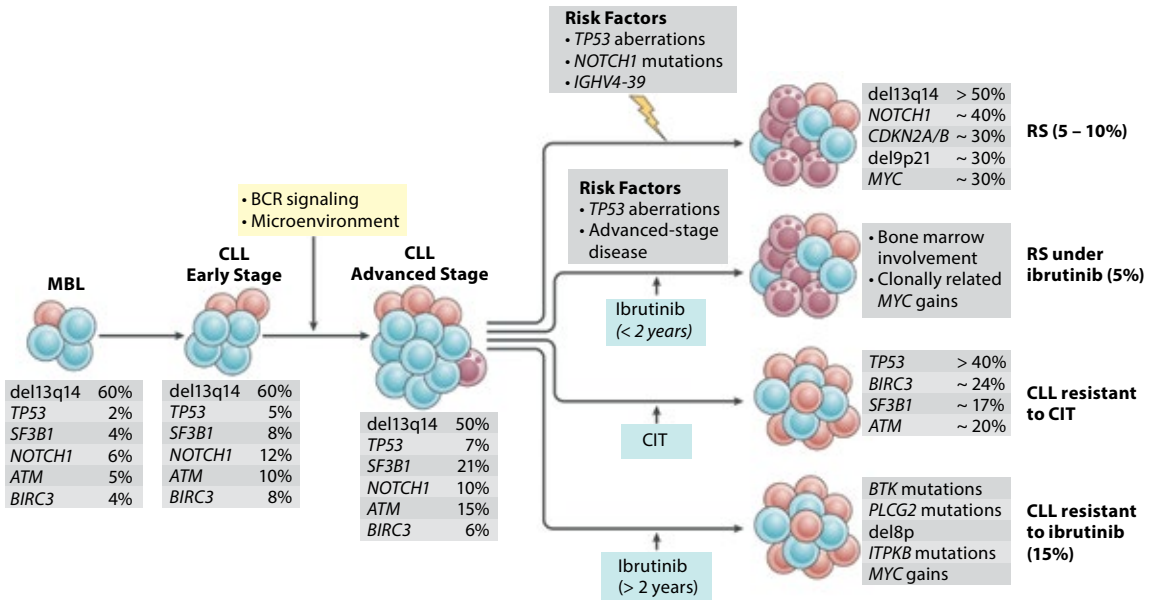
Type	Preferred First-Line	Selected Other Options
CLL with del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab Venetoclax + obinutuzumab Zanubrutinib*	Alemtuzumab ± rituximab Ibrutinib Obinutuzumab Ibrutinib + venetoclax (category 2B)
CLL without del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab (category 1) Venetoclax + obinutuzumab (category 1) Zanubrutinib (category 1)	Ibrutinib (category 1) FCR (fludarabine, cyclophosphamide, rituximab) – consider for IGHV-mutated CLL in patients aged < 65 years without significant comorbidities.

*Zanubrutinib is not FDA-approved for CLL but has been studied for this indication.

B cell receptor signaling drives CLL cell survival thus the various targeted treatments alter this signaling. Targeted treatment options include oral Bruton tyrosine kinase (BTK) inhibitors (e.g., ibrutinib, acalabrutinib, zanubrutinib), oral B cell lymphoma 2 inhibitor (venetoclax), and injectable anti-CD20 monoclonal antibodies (e.g., rituximab, obinutuzumab). First-line CLL treatment has shifted away from CIT based approaches which combine chemotherapy and anti-CD20 agents to oral targeted therapy because of survival advantages and fewer short- and long-term adverse events. The National Comprehensive Cancer Network (NCCN) recommendations for first-line treatment are summarized in Exhibit 2.[3]

Oral targeted therapies do not cure CLL but they can control CLL for many years. Ibrutinib has been the most commonly used first-line therapy of CLL and improves overall survival (OS) over chemotherapy and CIT in both older and younger patients.[5-7] The most recent update of the NCCN Guidelines now recommend acalabrutinib and zanubrutinib over ibrutinib (Exhibit 2).[3] Ibrutinib was moved from preferred regimens to other recommended regimens

Exhibit 3: Clonal Evolution[1]



MBL = monoclonal B-cell lymphocytosis; BCR = B-cell receptor; RS = Richter's Syndrome; CIT = chemoimmunotherapy

based on its toxicity profile compared to the other two next generation BTK inhibitors. The one comparison trial of acalabrutinib versus ibrutinib (Elevate RR) found the two agents noninferior with a median progression-free survival (PFS) of 38.4 months in both arms. All-grade atrial fibrillation/atrial flutter incidence was significantly lower with acalabrutinib versus ibrutinib (9.4% versus 16.0%; p = .02) and median overall survival was not reached in either arm.[8] In patients who are already taking ibrutinib with no intolerance, ibrutinib can be continued until disease progression.

Zanubrutinib is FDA-approved for the treatment of Waldenström's macroglobulinemia and relapsed/refractory mantle cell lymphoma. In the Alpine study, zanubrutinib was compared to ibrutinib in relapsed or recurrent CLL. The primary endpoint of overall response rate by investigator assessment was significantly higher in the zanubrutinib arm versus ibrutinib arm (78.3% versus 62.5%; p = .0006).[9,10] The 12-month landmark event-free rates for zanubrutinib versus ibrutinib were 94.9% versus 84.0%, respectively (p = .0007). At 12 months, overall survival (which was not a prespecified analysis) was not statistically different, at 97.0 percent with zanubrutinib and 92.7 percent with ibrutinib (p = .1081), reflecting 11 and 19 deaths, respectively. A lower rate of atrial fibrillation/flutter was observed with zanubrutinib (2.5% versus 10.1%; p = .0014) and major bleeding rates were also lower (2.9% versus 3.9%), as were adverse events leading to treatment discontinuation (7.8% versus 13.0%, respectively) or death (3.9% versus 5.8%). Neutropenia occurred more often with zanubrutinib (28.4% versus 21.7%). This trial has not yet been published in peer reviewed literature.

Venetoclax plus obinutuzumab is another option which is a fixed duration of treatment which may appeal to many patients. A BTK inhibitor is continued until disease progression and/or intolerance. Venetoclax regimens are typically given for one year and then patients are observed for relapse and retreatment indication once treatment ends. Combination venetoclax-based approaches demonstrate high rates of undetectable minimal residual disease (uMRD) providing potential for time-limited therapy. Optimal duration remains unclear but optimizing uMRD states should remain a goal for any time-limited therapeutic approach in CLL.

Second- and third-line therapy options are based on type of therapy received for first-line therapy and response to first-line therapy.[3] With treatment the B-cell clones evolve and there is divergence based on time, treatment, and underlying biology (Exhibit 3).[1] The evolution of the B-cell clones leads to therapy resistance and Richter's Syndrome, a rare complication characterized by the sudden transformation into a significantly more aggressive

form of large cell lymphoma.

The widespread adoption of targeted therapy has increased the costs of CLL care. These increases are driven by high medication prices, prolonged treatment duration with BTK inhibitors, and an increased number of patients living longer.

Conclusion

Improvement is needed in the prognostic workup and incorporation of information into treatment decision making. BTK inhibitors have demonstrated long-term efficacy and safety data with later generation agents demonstrating noninferior PFS and improved adverse event profiles. Later generation agents are replacing ibrutinib as preferred therapy. Venetoclax-based regimens offer patients a time limited treatment option but uMRD needs to be achieved for the longest duration of benefit.

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New Developments in the Treatment and Management of Chronic Cough: Managed Care Considerations on the Role of New and Emerging Therapies

Peter Dicpinigaitis, MD

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

Summary

Chronic cough has a significant impact on those affected and has a financial impact when not diagnosed in a timely manner. Effective therapies are currently lacking but at least one new class of medication is likely to be FDA-approved in the next year. Managed care will need to address appropriate utilization of this class.

Key Points

- Chronic cough causes significant quality of life impact.
- Many patients remain refractory to both disease-specific therapies and current cough-suppressing medicines creating a need for improved therapies.
- All patients with unexplained or refractory chronic cough will be appropriate candidates for a trial of a P2X3 antagonist once it becomes commercially available.

COUGH IS THE MOST COMMON COMPLAINT for which outpatients in the United States (U.S.) seek medical attention, leading to over 16 million outpatient visits annually.[1] An estimated $3.6 billion is spent annually on non-prescription cough and cold therapies in the U.S.[2] The economic implications of cough include the cost of over 16 million annual outpatient visits, plus diagnostic workups, prescription medications to treat cough, lost work and lost school productivity.

Although most cases of acute cough, primarily due to respiratory infections, are transient and self-limited, chronic cough often poses a diagnostic and therapeutic challenge.[3] Chronic cough is a debilitating condition that results in individuals coughing hundreds to thousands of times per day and is defined as a cough that lasts eight weeks or longer in adults, or four weeks in children.

Women are more likely to have chronic cough than men – probably because of gender-related

Exhibit 1:Diagnostic-Therapeutic Trials

Upper Airway Cough Syndrome
Oral first-generation antihistamine
Inhaled corticosteroids
Inhaled ipratropium
Asthma or Non-Asthmatic Eosinophilic Bronchitis
Oral corticosteroids
Inhaled corticosteroids
Leukotriene receptor antagonist
GERD
Acid-suppression therapy (high-dose proton pump inhibitor)
Anti-reflux lifestyle measures
Pro-kinetic agent (metoclopramide)

differences in cough reflex sensitivity.[4] Although chronic cough can occur at any age, the rate rises substantially in women who are 40 years of age or older but is highest in the 60 to 69 age group.[3] The highest rates in men are seen in the 50 to 59 and 60 to 69 age groups.

Chronic cough can have a significant health impact. Depression is common in those with chronic cough. One study has found a depression rate of 53 percent.[5] Improvement in cough correlates with improvement in depression score. Urinary incontinence is also common. Sixty-three percent of women with chronic cough report stress incontinence.[6] Most women are unaware that this is a common side event of chronic cough and will not volunteer this complaint unless specifically asked.

Chronic cough can also impact the ability to speak and for some to hold jobs that require a lot of speaking. The general approach to adults with chronic cough is to first rule out life-threatening conditions such as lung cancer, then to identify the obvious causes and treat accordingly. The primary causes of chronic cough are upper airway cough syndrome (formerly postnasal drip syndrome), asthma, non-asthmatic eosinophilic bronchitis, gastroesophageal acid reflux disease (GERD), angiotensin converting enzyme (ACE) inhibitor treatment, and smoking. Patient history, examination and a chest X-ray may suggest potential causes. Objective assessment to rule out the common causes includes tests for bronchial hyperresponsiveness and eosinophilic bronchitis, pulmonary function tests, swallowing tests, sinus imaging, high resolution chest computed tomograph (CT) scan, bronchoscopy, workplace and environmental assessment, and a cardiac evaluation. Some clinicians will recommend a trial of appropriate medication if a common cause is suspected (Exhibit 1). The American College of Chest Physicians (CHEST) Guidelines recommend not using these medications if diagnostic tests are negative because there is no proof of efficacy if those conditions are not present.[7] Despite thorough evaluation, approximately 10 percent of patients with chronic cough do not have an identifiable cause.

One major cost factor in managing chronic cough is the repetition of diagnostic tests. Motivated and desperate chronic cough patients seek evaluation from many physicians including primary care and specialists such as pulmonary, allergy, ear nose throat, and gastrointestinal. This can take place over decades, and in some cases years, with the hope of obtaining relief from their chronic cough. Great expense is generated by repetitive physician visits and diagnostic tests, many of which are repeated by new physicians, even though these tests may have been previously negative.

Therapy for chronic cough should be directed to the underlying cause where possible. Multi-modal therapy is often needed because chronic cough may have more than one cause in many patients (e.g., GERD plus smoking). In adult patients with unexplained chronic cough, the CHEST Guidelines suggest a therapeutic trial of multimodality speech pathology therapy (Grade 2C).[7] Behavioral interventions to suppress cough when the urge arises and avoiding triggers can effectively improve quality of life in patients with chronic cough.

In addition to treating underlying causes and speech therapy, pharmacologic treatment options aimed at cough in general are low dose narcotics (hydrocodone, codeine; morphine), amitriptyline, gabapentin, and pregabalin. Gabapentin is the only agent recommended by the CHEST Guidelines (up to 900 mg BID). Unfortunately, the current pharmacologic options are only effective and/or tolerated by a minority of patients. New, safe, and effective cough-targeting medications are desperately needed.

A variety of neuromodulatory pathways have been discovered that are involved in the cough reflex. For example, P2X3 receptor channels expressed in sensory neurons have been identified as serving important roles in nociception, sensory hypersensitization, and the cough reflex.[8] P2X3 receptor antagonists are one class of agents for unexplained or refractory chronic cough that are currently under investigation. Refractory chronic cough is one in which appropriate treatment for identified causes has not been effective in treating the cough.

Gefapixant, an investigational, non-narcotic, selective antagonist of the P2X3 receptor, is the closest to market. Its new drug application is currently under review by the FDA. The first world approval was in January 2022 in Japan.[9] Efficacy of gefapixant in reducing cough frequency was demonstrated in Phase II clinical trials in patients with unexplained or refractory chronic cough.[10,11] Dysgeusia was the most common adverse event in the Phase II trials, occurring in 5 percent on placebo, 10 percent on gefapixant 7.5 mg , 33 percent on 20 mg, and 48 percent on 50 mg. Dysgeusia is a known adverse event of this class of agents because P2X2/3 heterodimers have a major role in taste. Other adverse events were mild and not significant compared to placebo.

On the basis of Phase II data, two international Phase III, randomized, double-blind, placebo-

Exhibit 2: Unanswered Questions Related to P2X3-Receptor Antagonists

- Price
- Who will be allowed to prescribe?
  - All physicians
  - Only specialists (Pulmonary, Allergy, ENT)
- Will proof of sufficient work-up of chronic cough to verify diagnosis of *Refractory/Unexplained* chronic cough be required?
- How rigorous will the requirements be?
- Will trials of appropriate medications for Asthma, GERD, etc., be required before prescribing?
- How long will this medication be taken? Months, years, forever?

controlled trials, with combined enrollment exceeding 2,000 patients with unexplained or refractory chronic cough and with treatment durations of up to one year were begun (COUGH-1 and COUGH-2). The primary efficacy outcomes measure for both studies were 24-hour coughs per hour at week 12, and 24-hour coughs per hour at week 24. Secondary endpoints for both studies included awake coughs per hour. Coughs were measured using an ambulatory digital audio recording device. These two trials each had three treatment groups (gefapixant 45 mg twice daily, gefapixant 15 mg twice daily, or placebo).

Gefapixant 45 mg twice per day produced significant reductions in 24-hour cough frequency compared with placebo at week 12 in COUGH-1 (18.5%; $p = 0.041$) and at week 24 in COUGH-2 (14.6%; $p = 0.031$).[12] Gefapixant 15 mg twice per day did not show a significant reduction in cough frequency versus placebo in either study. The most common adverse event again was dysgeusia (16.2% and 21.1%) but ageusia, hypergeusia, and hypogeusia also occurred in low percentages. Overall, 65 percent and 81 percent of 45-mg subjects, respectively, experienced an adverse event related to taste. 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. The optimal dose which reduces cough effectively while minimizing taste issues is not yet known.

In addition to gefapixant, other P2X3 antagonists including eliapixant and sivopixant are under development. All patients with unexplained or refractory chronic cough will be appropriate candidates for a trial of a P2X3-antagonist, when it becomes commercially available, due to its relative safety and the lack of effective alternatives. Tolerability issues could be a significant factor if more than one product in the class receives approval. P2X3 and P2X2/3 are found on taste buds, suggesting a class-wide issue, but there is evidence the selectivity of molecules may affect the extent of taste disturbances.

There are several unanswered questions about how this class of agents should be managed once they are FDA-approved (Exhibit 2). Cost is a big unknown but will be significantly more than traditional cough medications, however, these lack efficacy for chronic cough. Managed care plans will have to decide initial formulary restrictions for this class. How long a P2X3 antagonist should be taken to manage chronic cough is another looming unanswered question. The Phase III trials were for one year and showed reasonable safety over this time period. It is not yet known if treatment for a period of time will "reset" a patient's cough reflex or if treatment will have to continue indefinitely.

Conclusion

Chronic cough is a significant problem. Many patients remain refractory to both disease-specific therapies and current cough-suppressing medicines creating a need for improved therapies. All patients with unexplained or refractory chronic cough will be appropriate candidates for a trial of a P2X3 antagonist once it becomes commercially available. The P2X3 antagonist pipeline is robust and potential indications for this class go far beyond chronic cough. Payers will need to consider who should be prescribing and when a P2X3 agent should be used.

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Evolving Considerations in the Treatment and Management of Metastatic Breast Cancer: Expert Strategies for Improved Clinical and Economic Outcomes

Gary M. Owens, MD

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

Summary

Certain inherited genetic mutations increase the risk of breast cancer by increasing the genetic instability in cells. Targeting these mutations with agents such as PARP inhibitors can increase progression-free survival in women with metastatic breast cancer who have these mutations. Unfortunately, this type of therapy has not yet been shown to improve survival.

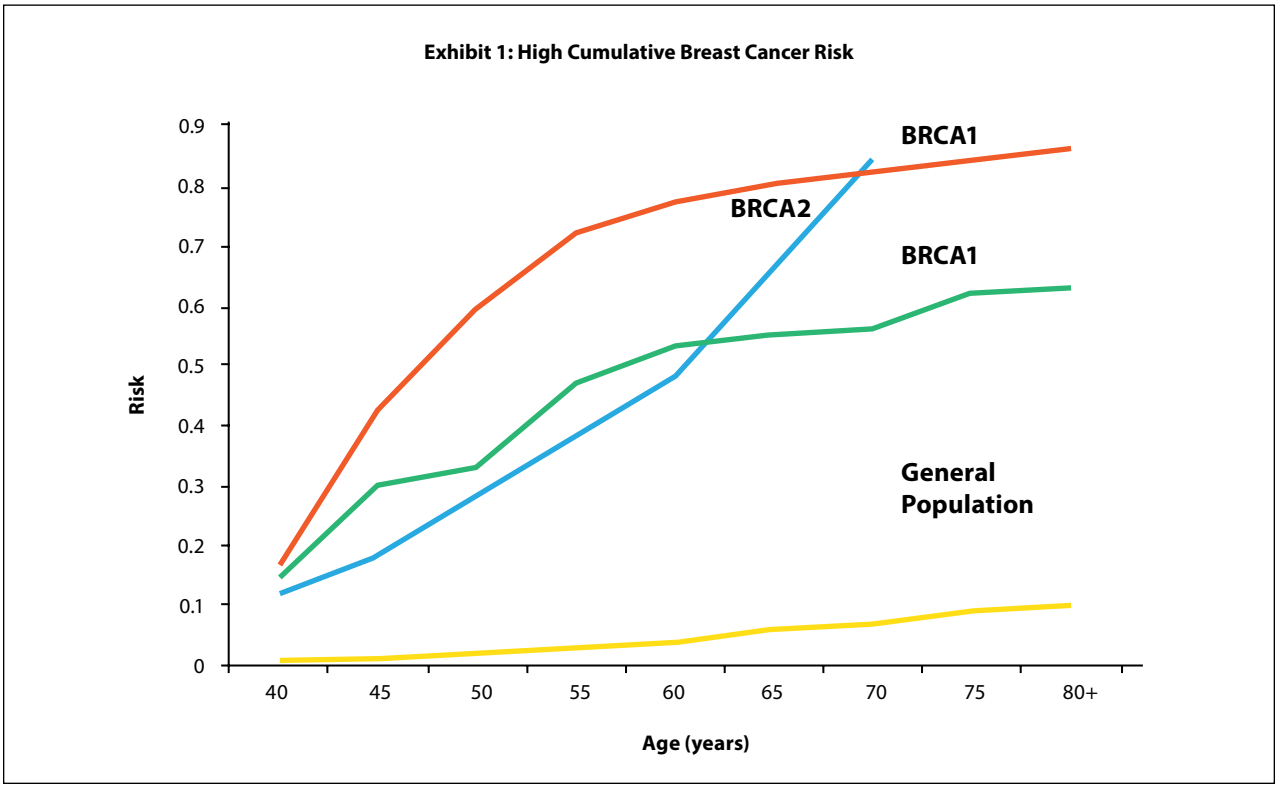
Key Points

- Women with germline (inherited) BRCA mutations have a significantly increased risk of developing breast cancer.
- PARP inhibitor monotherapy provides a statistically significant and clinically meaningful progression-free survival benefit versus standard-of-care chemotherapy for patients with HER2-negative metastatic breast cancer and a germline BRCA mutation.

AN ESTIMATED 12.9 PERCENT OF WOMEN born in the United States (U.S.) today will develop breast cancer at some time during their lives.[1] Some women are at higher risk of developing breast cancer because of breast cancer (BRCA) genetic mutations. Germline BRCA mutations occur in about 0.25 percent of the general population, excluding those of Ashkenazi Jewish descent.[2] In the Ashkenazi Jewish population, BRCA mutations occur in 2.5 percent in the overall population and in 10 percent of those with breast cancer. Two percent of women with breast cancer at any age and 10 percent of women with breast cancer who are younger than 40 years of age have BRCA mutations. Exhibit 1 compares the cumulative risk of breast cancer for those with BRCA1, BRCA2, and no BRCA mutation.[1,3-5]

Germline BRCA mutations lead to loss of function in genes implicated in DNA repair and cell-cycle checkpoint activation. BRCA mutation and hormone receptor status are interlinked.[6] Individuals with a gBRCA1 mutation are more likely to have triple-negative breast cancer (TNBC) than hormone receptor-positive (HR+) disease, whereas patients with gBRCA2 mutations tend to develop HR+ breast cancer. gBRCA mutations are found in up to 23 percent of patients with TNBC and in 5 percent of patients with HR+ disease.

Goals of treatment for patients with metastatic breast cancer include prolongation of survival, symptom relief, maintenance of quality of life, delay in needing treatments with untoward adverse events, and improved progression-free survival. Despite the plethora of treatment modalities available in metastatic breast cancer, significant survival differences are uncommon. Symptom relief as a goal is not used as widely as it should be. Progression-free survival is a measure that includes both patients who achieve an objective response, and those whose disease may be stabilized with treatment. Poly (ADP-ribose) polymerase (PARP)



inhibitors have become a part of the treatment of metastatic breast cancer in patients with BRCA mutations.

PARP is a versatile enzyme with several key physiological functions, among which is single-strand DNA break repair by base excision repair pathway. With PARP blockade by a PARP inhibitor, the single-strand breaks are not repaired and are converted into double-stranded breaks with cell replication.[7] The absence of functional BRCA and other homologous 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 a PARP inhibitor in breast cancer. PARP inhibition results in genomic instability and accumulation of damaged cells in cell cycle arrest.

The National Comprehensive Cancer Network (NCCN) Guidelines endorse germline BRCA1/2 mutation testing for all human epidermal growth factor receptor two (HER2) negative metastatic breast cancer (mBC) patients.[8] Although both olaparib and talazoparib are only FDA-approved for HER mBC, the NCCN Guidelines note that they support use in any breast cancer subtype that with gBRCA mutation.

Olaparib, talazoparib, niraparib, and rucaparib are all FDA-approved PARP inhibitors for several types of cancers with homologous repair deficiencies (HRD) but only olaparib and talazoparib are indicated for mBC. Olaparib was FDA-approved for treating gBRCA mutated mBC based on results from a Phase III trial (OlympiAD) that included subjects who had HER2 negative, gBRCA mutated mBC treated with no more than two prior lines of chemotherapy. Olaparib 300 mg twice a day was compared to standard-of-care chemotherapy (capecitabine, eribulin, or vinorelbine). Median progression-free survival (PFS) was significantly longer in the olaparib group than in the chemotherapy group (7.0 months versus 4.2 months; $p < 0.001$).[9] Final median overall survival (OS) was 19.3 months with olaparib versus 17.1 months with chemotherapy which was not statistically significant.[10] Olaparib was better tolerated than chemotherapy and those who received olaparib had better quality of life. Patients who had not had prior chemotherapy in the metastatic setting achieved a 7.9 month longer median survival with olaparib than those who received chemotherapy.[8] Importantly this trial had the wrong control arm – it should have been carboplatin or another platinum-

containing regimen. Overall, olaparib monotherapy provided a significant benefit over standard therapy with a better median PFS but not a survival benefit.

Talazoparib was evaluated in the Phase III EMBRACA trial in which subjects had no more than three prior lines of chemotherapy but had to have been treated with a taxane and anthracycline. Talazoparib 1 mg once a day was compared to standard-of-care chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Median PFS was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months versus 5.6 months; $p < 0.001$).[11] Median OS was 19.3 months with talazoparib versus 19.5 months which, similar to olaparib, was not statistically significant.[12] The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% versus 27.2%; $p < 0.001$). As with olaparib, single-agent talazoparib provided a significant benefit over standard chemotherapy with respect to PFS and was well tolerated.

A Bayesian fixed-effects indirect treatment comparison (ITC) analysis of data from the olaparib and talazoparib studies suggested no significant difference in PFS efficacy between olaparib and talazoparib.[13] However, there were differences in specific adverse events; patients receiving olaparib had a higher rate of nausea and vomiting, while those receiving talazoparib had a higher rate of alopecia and anemia. These two agents have not been directly compared to each other nor is there published real-world efficacy data.

Given the cost of PARP inhibitors, managed care plans may look to choose one agent over another to achieve better pricing. In addition to the acquisition cost, the cost of managing adverse events also needs to be accounted for in any decision. Based on the reported rate of Grade 3 and 4 adverse events in the clinical trials, managing these adverse events in mBC was estimated at $3,574 for olaparib and $9,489 for talazoparib.[14] Hematological toxicities were the key drivers of adverse event management costs in this analysis. Researchers recently presented an analysis of the potential cost-saving benefits of switching breast cancer patients from olaparib to talazoparib in an Academy of Managed Care Pharmacy eLearning Days poster session. The authors concluded that adding talazoparib to a U.S. commercial health plan with one million members and with half of the mBC patients starting talazoparib in lieu of olaparib would result in a decrease of treatment costs of $35,658 and an increase in adverse event management costs of $5,239. This corresponded to potential incremental cost-savings of $242 per treated member per month.[15] While the study shows promising results Dr. Arondekar and colleagues concluded that future studies will be necessary to further to validate the results using real-world U.S. health plans' data.

In non-U.S. based analyses, PARP inhibitor therapy has not met current defined criteria for cost-effectiveness due to high cost, lack of overall survival benefit, cost for BRCA-mutation testing (including family members), and the expense of managing toxicities (e.g. blood transfusion).[16] Although likely not cost effective in the U.S., most managed care plans are covering these agents for appropriate populations.

PARP inhibitors are being investigated for the treatment of BC in patients with HRD mutations other than BRCA or with somatic (acquired) BRCA mutations. Additional agents including veliparib may also reach the market. Other directions for evaluation of PARP inhibitors include use in earlier stages of the disease and in combination with agents that target other HRD-related pathways, with a view to potentially avoiding resistance to PARP inhibitor therapy and expanding indications beyond the gBRCA mutated population.

Conclusion

PARP inhibitor monotherapy provides a statistically significant and clinically meaningful PFS benefit versus standard-of-care chemotherapy for patients with HER2-negative metastatic breast cancer and a gBRCA mutation. PARP inhibitors do not meet current defined criteria for cost-effectiveness due to high cost, lack of overall survival benefit, cost for BRCA-mutation testing (including family members), and the expense of managing toxicities (e.g., blood transfusion). Nevertheless, there is enthusiasm to use PARP inhibitors for gBRCA-mutated tumors on the part of treating oncologists, as well as recognition by guideline committees and regulators.

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Recent Advances in the Treatment and Management of Heart Failure: Expert Perspectives on the Role of New and Emerging Therapies

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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

Heart failure (HF) continues to be a major public health issue in the United States. Several new classes of medications are now available for reducing hospitalization and death related to HF. Managed care has a role in ensuring that guideline directed therapy is instituted in those with HF and that patients have support to be adherent with their oftentimes complicated medication regimens.

Key Points

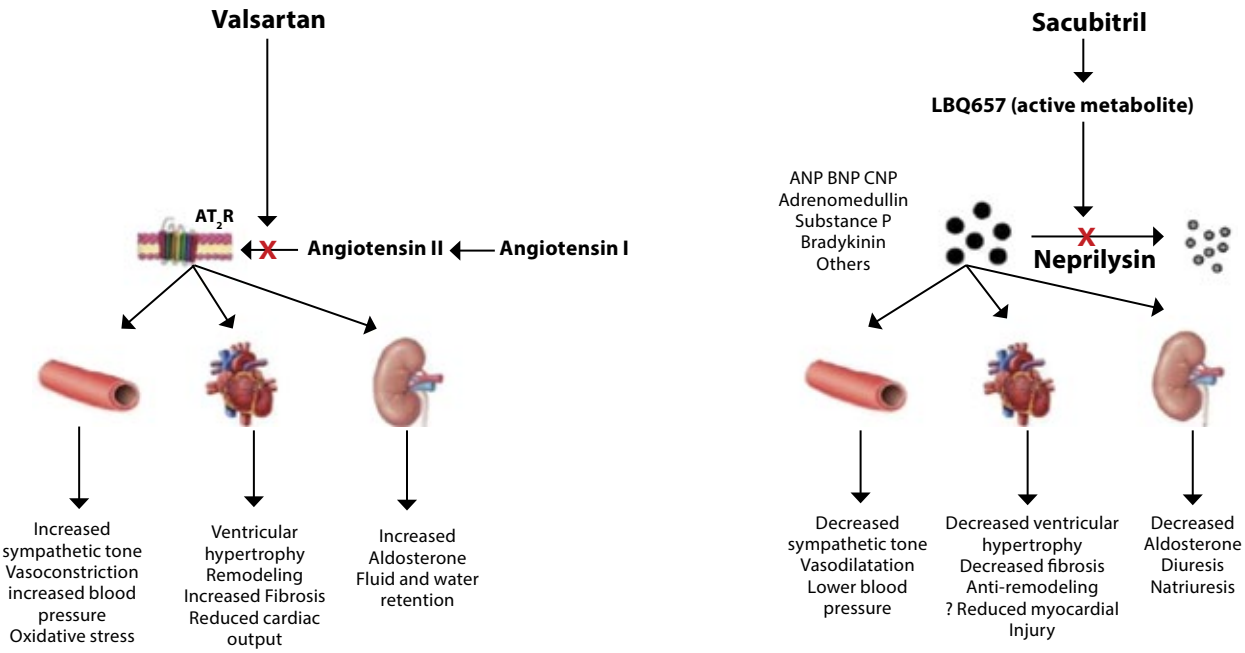
- Novel therapies reduce heart failure hospitalization and mortality and their benefits extend beyond heart failure with reduced ejection fraction (HFrEF).
- The angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter-2 (SGLT2) inhibitors are recommended as step 1 therapies for those with HFrEF Stage C disease.
- Medication adherence interventions and outpatient diuresis centers can also improve outcomes in HF management.

HEART FAILURE (HF) IS A SIGNIFICANT public health issue in the United States (U.S.) that affects 6.5 million adults. The lifetime risk for HF is one in five after age 40 and the five-year mortality is 50 percent for those over age 80. The total of direct medical costs in the U.S. was $30.7 billion in 2012 and it is projected to increase to $69.7 billion by 2030. The mortality rates and hospitalization for HF remained stable from 2006 to 2014, however, emergency room visits increased during that period.[1] Factors contributing to HF-related hospitalizations and total cost include concomitant diseases of hypertension (72% of patients), coronary artery disease (56%), diabetes (48%), chronic kidney disease (47%), and atrial fibrillation (43%). HF can occur with reduced left ventricular ejection fraction (LVEF) (HFrEF) or preserved LVEF (HFpEF). Reduced LVEF is defined as EF less than 50 percent and it is important to note that the major medication trials have used less than 45 percent. The primary focus of this article is HFrEF.

Several therapies have been added to the HFrEF treatment armamentarium in recent years – an angiotensin receptor/neprilysin inhibitor (ARNI), sodium glucose co-transporter 2 (SGLT2) inhibitor, and a soluble guanylate cyclase (sGC) stimulator. Sacubitril/valsartan is the only available ARNI. Exhibit 1 shows the benefits of these, combining angiotensin receptor blocking and neprilysin inhibition. In the PARADIGM HF trial which compared this combination to enalapril, the ARNI was associated with a reduction in cardiovascular death or hospitalization for HF compared to enalapril (4.7% absolute reduction in risk).[2] Subjects in this trial had reduced EF (< 40%) and New York Heart Association (NYHA) Class II to IV symptoms. Sacubitril/valsartan is FDA-approved to reduce the risk of cardiovascular death and hospitalization for HF in adult patients with chronic heart failure. Benefits are most clearly evident in patients with LVEF below normal.

The SGLT2 inhibitor class, which increases renal excretion of glucose, was originally developed for and FDA-approved to treat type 2 diabetes (T2D). Large-scale cardiovascular outcomes trials, which are required by the FDA for any new agents

Exhibit 1: Benefits of Sacubitril/Valsartan



for T2D, found that these agents reduce risk of primary and secondary hospitalization due to HF and cardiovascular death even in diverse subsets of patients with T2D regardless of cardiovascular disease history. Independent of glucose control, SGLT2 inhibitors exert pleiotropic metabolic and direct cardioprotective and nephroprotective effects which help explain the cardiovascular benefits.[3] SGLT2 inhibition also reduces inflammation, oxidative stress, fibrosis, intraglomerular hypertension, and sympathetic nervous system activation, and may improve mitochondrial function and myocardial efficiency.

Trials were also done in patients without T2D. Data from the Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure (DAPA-HF) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced) have demonstrated the positive clinical impact of SGLT2 inhibition in patients with HFrEF both with and without T2D.[4,5] These data have led to the FDA approval of dapagliflozin and empagliflozin for the treatment of patients with HFrEF, irrespective of T2D status.

The benefits of SGLT2 inhibitors are also being evaluated in HFpEF. In a trial with empagliflozin (EMPEROR-preserved), the SGLT2 inhibitor reduced the combined risk of cardiovascular death or hospitalization for HF in patients with HFpEF, regardless of the presence or absence of diabetes.[6] The primary outcome, cardiovascular death, or HF hospitalization, for empagliflozin compared to placebo was 13.8 percent versus 17.1 percent ($p < 0.001$). The benefit was primarily driven by a reduction in HF hospitalizations, not mortality.[7] There was also a benefit in estimated kidney function (eGFR), but not in renal outcomes per se; renal benefits of SGLT2 inhibitors appears to primarily be in those with HFrEF. Empagliflozin improved quality of life measures, and the improvement was seen early and was sustained for one year.

Vericiguat, an oral soluble guanylate cyclase (sGC) stimulator, increases sGC activity to improve myocardial and vascular function. In the heart, vericiguat therapy leads to a decrease in progressive myocardial stiffening and thickening, decrease in ventricular remodeling, and decrease in fibrosis. In the vasculature, there is then decreased arterial constriction and vascular stiffness. VICTORIA was a Phase III trial that compared vericiguat, at a target dose of 10 mg, with placebo in 5,050 patients with HFrEF (ejection fraction < 45%) on top of guideline-directed medical therapy (GDMT). The composite endpoint was the first occurrence of cardiovascular

Exhibit 2: Contemporary Clinic Trials in HFrEF[2,5,6,10]

Characteristic	PARADIGM-HF (Sacubitril/Valsartan)*	DAPA-HF (Dapagliflozin)	EMPORER-Reduced (Empagliflozin)	VICTORIA (Vericiguat)
Median follow up months	27	18	16	11
Mean EF, %	29	31	27	29
Mean eGFR mL/min/1.73 m^2	68	66	62	61
AF/NYHA III – IV, %	37 / 25	38 / 33	37 / 25	45 / 41
Median NT-proBNP, pg/mL	1,615	1,437	1,910	2,816
Primary endpoint, HR (95% CI)	0.80 (0.73 to 0.87)	0.74 (0.65 to 0.85)	0.75 (0.65 to 0.86)	0.90 (0.82 to 0.98)
• CV death	0.80 (0.71 to 0.89)	0.82 (0.69 to 0.98)	0.92 (0.75 to 1.12)	0.93 (0.81 to 1.06)
• First HFH	0.79 (0.71 to 0.89)	0.70 (0.59 to 0.83)	0.69 (0.59 to 0.81)	0.90 (0.81 to 1.00)

EF = ejection fraction; eGFR = estimated glomerular filtration rate; AF = atrial fibrillation; NYHA = New York Heart Association; NT-proBNP = N-terminal-pro hormone B-type natriuretic peptide; HR = hazard ratio, CV = cardiovascular; HFH = heart failure hospitalization

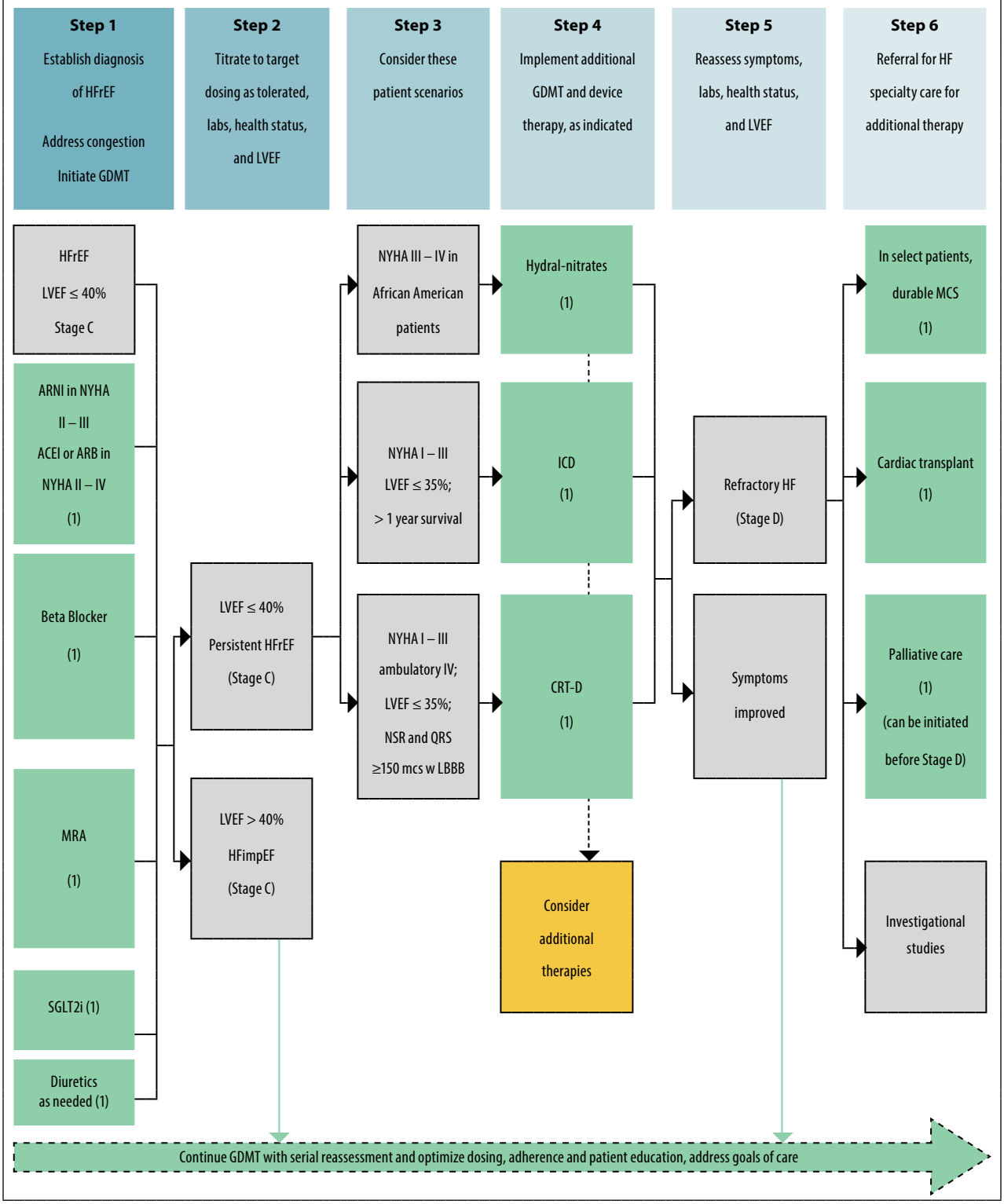
death or hospitalization for HF. The median follow up was 10.8 months. The included patients had to have had a HF-related hospitalization or need of intravenous (IV) diuretic therapy in the preceding six months, making it a particularly high-risk and vulnerable patient population. Mortality following hospitalization for patients with HF is as high as 30 percent within one year.[8,9] The composite endpoint occurred less frequently with vericiguat than with placebo (35.5% versus 38.5%, $p = 0.02$).[10] The number needed to treat with vericiguat from this trial is 24. This agent is now FDA-approved to reduce the risk of cardiovascular death and HF hospitalization following a hospitalization for HF or need for outpatient IV diuretics, in adults with symptomatic chronic HF and EF less than 45 percent.

Compared to the other recent large trials in HFrEF, patients in VICTORIA were older, more symptomatic (up to 40% NYHA III to IV class), had higher N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) levels, and were more vulnerable since 84 percent had been hospitalized for heart failure in the previous six months.[11] Exhibit 2 compares the recent trials.[2,5,6,10] Vericiguat may be a drug of choice in the highest-risk patients with recent or recurrent hospitalizations despite full background medication. The drug has also shown safety in patients with reduced renal function.

The American College of Cardiology/American Heart Association/Heart Failure Society of American (ACC/AHA/HFSA) guidelines for managing heart failure were updated in 2022. The guideline algorithm for HFrEF Stage C (LVEF < 40%) is shown in Exhibit 3; step 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF.[12] Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication. Medication doses should be increased to target as tolerated. The guidelines recommend ARNI over angiotensin converting enzyme inhibitors or angiotensin receptor blockers alone in NYHA II to III, if possible, and the guidelines note that this choice of therapy provides economic value. In patients with symptomatic chronic HFrEF, an SGLT2 inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of T2D, and also provide economic value. In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, vericiguat may be considered. The ACC/AHA/HFSA guidelines note that in patients with HFpEF, a SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality and an ARNI may be considered in selected patients with HFpEF to decrease hospitalizations, particularly among patients with LVEF on the lower end of the spectrum.

In addition to maximizing use of these newer agents, certain patients are at an elevated risk for worsening HF and should be identified for prompt intervention to prevent life-threatening events. Iron deficiency anemia is one comorbidity which can contribute to worsening disease and should be treated. Intravenous iron replacement improves patient global assessment, NYHA class, and exercise capacity.[13] It has also been shown to reduce the

Exhibit 3: ACC/AHA Recommendations HFrEF Stage C[12]



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker;
ARNI = angiotensin receptor-neprilysin inhibitor; CRT = cardiac resynchronization therapy;
GDMT = guideline-directed medical therapy; ICD = implantable cardioverter-defibrillator;
Hydral-nitrates = hydralazine and isosorbide dinitrate; HFrEF = heart failure with reduced ejection fraction;
LBBB = left bundle branch block; MCS = mechanical circulatory support; LVEF = left ventricular ejection fraction;
MRA = mineralocorticoid receptor antagonist; NSR = normal sinus rhythm; NYHA, New York Heart Association;
SGLT2i = sodium-glucose cotransporter 2 inhibito

risk of rehospitalizations in those whose iron deficiency was identified and corrected during a HF hospitalization.[14]

Hypertension also complicates HF management. Patients with HFrEF and hypertension should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg. Patients with HFpEF and persistent hypertension after management of volume overload should also be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg.

In addition to ensuring that patients with HF are on appropriate medications to maximize therapeutic outcomes, managed care should have a role in helping patients be adherent with their oftentimes complicated medication regimens. Inadequate adherence leads to increased HF exacerbations, reduced physical function, and higher risk for hospital admission and death. Interventions to improve medication adherence among HF patients have significant effects on reducing readmissions and decreasing mortality.[15] Telemonitoring with specific instructions to the patient to increase medication based on weight gain or blood pressure elevation is an effective adherence intervention.

Outpatient IV diuresis clinics which can help avoid the cost of emergency room visits and hospitalizations are an option for maximizing HF outcomes. One small trial found significant cost savings and equivalent efficacy and safety of outpatient IV diuresis compared to inpatient.[16]

Conclusion

Novel therapies reduce HF hospitalization and mortality and their benefits extend beyond HFrEF. The ARNI and SGLT2 inhibitors are recommended as step 1 therapies for those with HFrEF Stage C disease. Medication adherence interventions and outpatient diuresis centers can also improve outcomes in HF management.

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Evolving Considerations in the Management of Metastatic Head and Neck Squamous Cell Carcinoma: Expert Strategies on Immune Checkpoint Inhibitors

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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

The treatment of metastatic head and neck squamous cell cancer (HNSCC) has changed dramatically in recent years from just chemotherapy to chemoimmunotherapy. The combination of platinum-based chemotherapy and checkpoint inhibitor immunotherapy is providing survival benefits in this incurable disease state.

Key Points

- Pembrolizumab and nivolumab are both options for the treatment of platinum refractory metastatic HNSCC.
- Pembrolizumab/platinum/5-flurouracil or pembrolizumab monotherapy (with CPS ≥ 20) are preferred first-line regimens for recurrent, unresectable, or metastatic non-nasopharyngeal head and neck cancers.
- Novel checkpoint inhibitors are also under investigation and are the immunotherapy wave of the future.

HEAD AND NECK CANCER IN THE UNITED States (U.S.) accounts for about 4 percent of all cancers.[1] In 2022, an estimated 66,470 new cases and 15,050 deaths will occur.[1] Males are affected significantly more often than females. Head and neck cancers may present in a variety of sites including the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands. Ninety-five percent of cases are of squamous cell origin, [head neck squamous cell carcinoma, (HNSCC)].

Risk factors for HNSCC are tobacco use, alcohol use, and viral infections.[2-4] Tobacco use increases risk five- to 25-fold with risk dependent on exposure amount and duration. Smokeless tobacco products are especially a risk for oral cavity and pharynx cancers. Alcohol use increases risk five- to six-fold but risk from alcohol is often difficult to distinguish from the risk of using tobacco because these risk factors typically occur together. Viral infections (Epstein Barr, human papilloma virus (HPV), herpes simplex, and hepatitis C), immunodeficiency, occupational exposure, and radiation are also risk factors. HPV is involved in the etiology of 60 to 80 percent of oropharyngeal cancer in the U.S. and primarily results in base of tongue and tonsil cancers.[5] Ninety percent of HPV positive cases are due to HPV16.[6]

While many patients with locally advanced disease are cured with some combination of surgery, radiation, and chemotherapy, those with metastatic disease are considered incurable. Treatment options for metastatic HNSCC include chemoimmunotherapy, immunotherapy, or various chemotherapy regimens.

Anti-programmed death one (PD-1) checkpoint

Exhibit 1: Pembrolizumab or Pembrolizumab/Platinum/5FU (Pembro+Chemo) versus Cetuximab/Platinum/5FU (Extreme)[11]

	Pembro	Extreme	Pembro+Chemo	Extreme
PD-L1 CPS ≥ 20				
Median OS, months	14.7	10.8 ($p = 0.00034$)	14.7	11.1 ($p = 0.00082$)
24-month OS	35.3%	19.7%	35.4%	20.0%
48-month OS	21.6%	8.0%	28.6%	6.6%
PD-L1 CPS ≥1				
Median OS, months	12.3	10.3 ($p = 0.0008$)	13.6	10.6 ($p = 0.00001$)
24-month OS	28.9%	17.7%	21.8%	17.1%
48-month OS	16.7%	5.9%	28.6%	4.1%

OS = overall survival; CPS = combined positive score; PD-L1 = programmed death ligand one

immunotherapy has become established as a standard of care in recurrent or metastatic HNSCC. Based on positive results of immunotherapy in Phase II trials, two randomized Phase III studies showed the benefits in platinum refractory recurrent or metastatic HNSCC. In CHECKMATE 141, treatment with the PD-1 inhibitor nivolumab was associated with a significantly longer overall survival (OS), – 7.5 versus 5.1 months, $p = 0.01$ – with less toxicity compared to investigator's choice of docetaxel, cetuximab or methotrexate.[7,8] The one-year survival rate was 34.0 versus 19.7 percent. In KEYNOTE 040, at the time of the preplanned survival analysis, the median OS was 8.4 months for pembrolizumab and 6.9 months for investigator's choice of docetaxel, cetuximab, or methotrexate.[9] While this result did not meet the pre-specified cutoff for survival improvement, longer follow-up has demonstrated a statistically significant improvement in OS. Based upon these data, both pembrolizumab and nivolumab have been approved by the FDA for the treatment of platinum refractory metastatic HNSCC.

Chemoimmunotherapy is one way to improve response rates to immunotherapy. In KEYNOTE 048, patients with untreated recurrent or metastatic HNSCC were randomized to pembrolizumab monotherapy, platinum/5-fluorouracil/cetuximab (the EXTREME regimen), or platinum/5-fluorouracil/pembrolizumab.[10] Pembrolizumab with chemotherapy improved OS versus platinum/5-fluorouracil/cetuximab in the total population, the programmed death ligand one (PD-L1) combined positive score (CPS) of 20 or more population, and CPS of 1 or more population.[10] In the long-term follow-up, 24- and 48-month OS rates with pembrolizumab were better in all groups versus platinum/5-fluorouracil/cetuximab (Exhibit 1).[11] Pembrolizumab combined with platinum/5-fluorouracil also produced better 24- and 48-month OS rates compared to the regimen without pembrolizumab.[11] Thus, for metastatic or advanced HNSCC without prior exposure to systemic therapy, the combination of pembrolizumab plus chemotherapy improves OS beyond that seen with cetuximab plus chemotherapy. For those with high PD-L1 expression, single-agent pembrolizumab also improves OS, compared with cetuximab plus chemotherapy, and with less toxicity. Responses to pembrolizumab, either alone or in combination with chemotherapy, are more durable than those seen with cetuximab plus chemotherapy. In 2019, the FDA approved the use of pembrolizumab for this indication along with cisplatin and fluorouracil and as a single agent for those whose tumors express PD-L1 CPS ≥ 1. The National Comprehensive Cancer Network (NCCN) Guidelines recommend pembrolizumab/platinum/5-flurouracil or pembrolizumab monotherapy (with CPS ≥ 20) as Category 1 preferred first-line regimens for recurrent, unresectable, or metastatic non-nasopharyngeal head and neck cancers.[12] Pembrolizumab monotherapy is also a first-line option when CPS is 1 to 19 but is not a Category 1 recommendation. Nivolumab is a Category 1 subsequent-line option if there is disease progression on or after platinum therapy. First-line therapy in the NCCN Guidelines for recurrent, unresectable, oligometastatic or metastatic nasopharyngeal cancer is cisplatin/gemcitabine. Nivolumab and pembrolizumab are

Category 2B recommendations for subsequent-line therapy for this type of cancer.

Other combinations for recurrent/metastatic HNSCC are being evaluated. Pembrolizumab is being studied in combination with cetuximab and showing good results. This regimen would be less toxic than pembrolizumab plus platinum/5FU. It is also being studied in combination with lenvatinib, a vascular endothelial growth factor (VEGF) receptor inhibitor.

A new target being explored is CD47 which inhibits macrophage phagocytosis and is highly expressed in HNSCC. The CD47 pathway is another way cancers evade the immune system.[13] Evorpacept (ALX48) targets CD47 to maximize phagocytosis of cancer cells and activate the adaptive immune system and is being studied in combination with other checkpoint inhibitor immunotherapies in various cancers. A trial with evorpacept plus pembrolizumab as a second-line or later treatment in those with HNSCC who progressed on prior platinum is ongoing.

Monalizumab and cetuximab are being studied in combination for HPV positive HNSCC. Monalizumab is a novel checkpoint inhibitor of NKG2A. This receptor is expressed on cytotoxic lymphocytes, including natural killer (NK) cells and subsets of activated CD8+ T cells. This mechanism of action unleashes NK cells in addition to T cells to kill cancer cells.

Conclusion

Anti-PD-1 immunotherapy has become a standard of care for first-line or later-line therapy in recurrent or metastatic HNSCC. There is promising data emerging for various combinations of immunotherapy and other agents. Novel checkpoint inhibitors are also under investigation and are the immunotherapy wave of the future.

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Innovations in Managing Pulmonary Arterial Hypertension Across the Evolving Treatment Landscape

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Summary

The prognosis for patients with pulmonary arterial hypertension (PAH) has progressively improved, from a time when no specific drug treatment was available, up to the current era, in which multiple drugs are now available and frequently employed in combination. Median survival has significantly increased but PAH remains an incurable and fatal disease.

Key Points

- Combination therapy with two different mechanisms of action is standard first-line treatment.
- Triple therapy is an option for high-risk patients.
- Survival is improved with therapy but the disease is not cured.

PULMONARY ARTERIAL HYPERTENSION (PAH) is a rare subtype of pulmonary hypertension (PH) and is a progressive disease of the small pulmonary arteries. It is characterized by elevated pulmonary artery pressure, worsening right-sided heart failure, decreasing functional status, and poor survival. It primarily affects women 30 to 60 years of age and is a fatal disease. The two-year survival rate without treatment is 50 percent. Exhibit 1 shows the prevalence of PAH by underlying cause.[1] Idiopathic PAH (IPAH) is the most common.

As the disease worsens, a steady rise is seen in peripheral vascular resistance (PVR) and pulmonary arterial pressure (PAP) in order to sustain cardiac output (CO). As long as the right ventricle is able to compensate for the resistance, PAP continues to increase as PVR increases. The increased right ventricle work-load causes it to hypertrophy and its efficiency falls, right heart failure ensues, and PAP will fall as the patient decompensates. Failure to maintain CO leads to shortness of breath, chest tightness, dizziness, and syncope, especially with activity. Unfortunately, the disease can be quite advanced before it is diagnosed.

PAH should be suspected in a patient with unexplained dyspnea. Initial screening should be an echocardiogram and tests for other diseases, such as asthma, which might account for the symptoms. If these tests suggest PAH, the patient should be referred to a PH expert for diagnosis with right heart catheterization.[2] However, many patients referred to PH expert centers may not even have PAH. In one study, 39 percent of patients initiated on PAH-specific medication prior to referral did not have PAH upon appropriate testing.[3]

The FDA-approved PAH specific medications target three of the known signaling pathways in PAH – endothelin, nitric oxide, and prostacyclin (Exhibit 2). All the approved therapies have been demonstrated to improve exercise capacity and New York Heart Association functional class. These improvements are associated with improvement in pulmonary hemodynamics (increased cardiac output, decreased peripheral vascular resistance).

Treatment is tailored according to a patient's risk profile as defined by certain, prespecified determinants of prognosis (Exhibit 3).[4] Assessment of prognosis for each individual patient is based on clinical variables such as cardiovascular hemodynamics and patients are classified into three

Exhibit 1: Prevalence of Group 1 PAH[1]

CONDITIONS	PREVALENCE
PAH	15 per million
IPAH	5.9 per million
HPAH	28 – 100 U.S. families*
Scleroderma	8.0% – 26.7%
Portopulmonary hypertension	1.0% – 6.0%
Congenital heart disease	1.6 - 12.5 per million
HIV	0.5% estimate
Sickle cell disease	32%
Schistosomiasis	11.8% – 80.0%
Chronic hemolytic anemia	Highly variable

IPAH = idiopathic pulmonary arterial hypertension; HPAH = hereditary pulmonary arterial hypertension

Note: Numbers may also reflect differences in diagnostic criteria (e.g., ECHO versus right heart catheterization) and study design (e.g., retrospective versus prospective).

* Number likely much higher, numerous genes have been identified which increase risk of PAH

risk categories (low, intermediate, and high) for death within one year.[5] Sequential therapy starting with one agent used to be the standard of care but this has evolved into combination therapy with at least two agents as initial therapy for most patients. Combination therapy targeting two or more pathways is now proven to provide better outcomes including better survival and is the best strategy for most patients.[6,7] For some low-risk patients, there is still a minor role for initial monotherapy. For those at high-risk, clinicians should start a combination that includes an intravenous prostanoid rather than two oral agents and consider starting with triple-combination therapy.

Triple-combination therapy that simultaneously impacts the three major pathophysiological pathways of PAH at the earliest possible point after diagnosis may be optimal but it is costly.[8] In one study of the survival benefits of a triple-combination regimen consisting of epoprostenol, bosentan, and sildenafil in PAH patients with severe disease (New York Heart Association functional class III/IV and severe hemodynamic impairment), all patients who started PAH treatment with upfront triple-combination therapy were still alive after a mean follow-up of 41.2 months.[9] Survival at one, two, and three years was 100 percent.

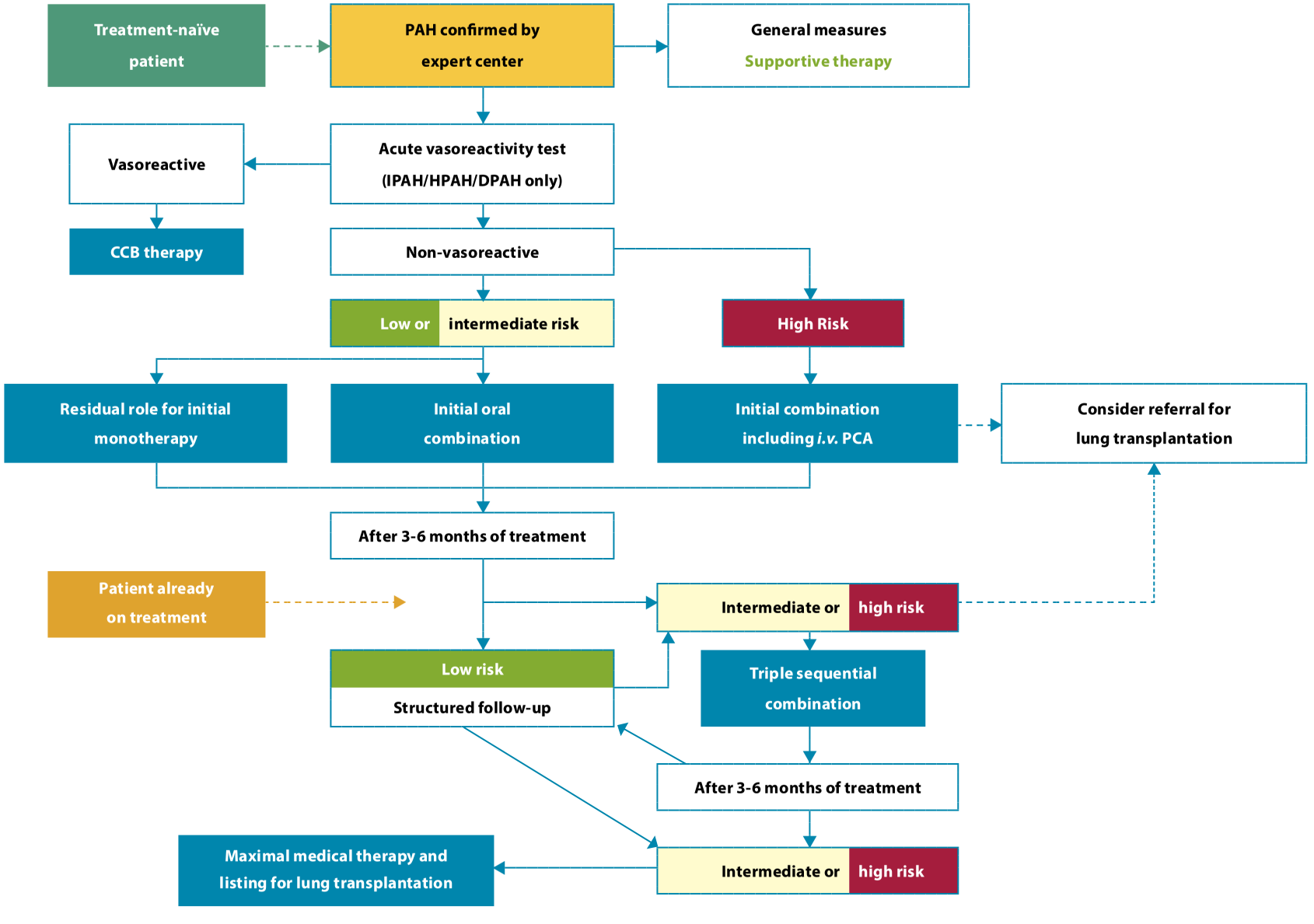
One goal of PAH treatment is to achieve low-risk status in order to maximize survival. The more categories of determinants of prognosis the patient has in the low-risk category the better their survival. Adjusting doses of a given medication and adding additional medications are all ways to optimize therapy. Especially for the intravenous and subcutaneous prostanoids the "correct" dose is not the same for every patient and must be individually titrated.[10] It may take some time to arrive at the optimal prostanoid dose. Importantly, a patient has not failed PAH treatment until they have failed individualized dosing of prostanoids. Initiation and optimization of a prostanoid dose is complex and best left to specialty PAH referral centers. Additionally, PAH is a progressive disease so therapy may need to change over time.

Several additional pharmaceuticals are under study for PAH. For example, ralinepag is a next generation, orally available, non-prostanoid, selective, and potent prostacyclin receptor agonist being studied in an extended-release formulation. It is currently in Phase III trials. Another agent in Phase II trials is sotatercept, a selective ligand trap for members of the transforming growth factor-beta superfamily to rebalance bone morphogenetic

Exhibit 2: PAH Specific Treatments

Prostacyclin Pathway	Endothelin Pathway	Nitric Oxide Pathway
Prostacyclin Analogues	**Endothelin antagonists**	**PDE-5 inhibitors**
• epoprostenol (IV)	• bosentan (oral)	• sildenafil (oral)
• iloprost (inhaled)	• ambrisentan (oral)	• tadalafil (oral)
• treprostinil (IV, SQ, inhaled, oral)	• macitentan (oral)	**Soluble guanylate**
• selexipag (oral)		• riociguat (oral)

Exhibit 3: PAH Treatment Algorithm[4]



protein receptor two (BMPR-II) signaling, which is a key molecular driver of PAH. BMPR loss of function genetic mutations have been identified as risk factors for PAH. Twenty-five to 30 percent of patients diagnosed with idiopathic PAH have an underlying genetic cause for their condition and should be classified as heritable PAH (HPAH).[11] In 2019 and 2020, the FDA granted Orphan Drug and Breakthrough Therapy designations, respectively, for sotatercept in the treatment of patients with PAH but it has not yet been FDA-approved.

One non-pharmaceutical treatment of PAH is bilateral lung transplantation. With lung transplantation, there is a narrow window of opportunity when the patient is sick enough but not too sick. Transplant is generally reserved for failure of optimal medical therapy. Data from the Registry of the International Society for Heart and Lung Transplantation have demonstrated that for primary transplant patients with idiopathic PAH who survived to one-year, conditional median survival was 10 years.[12]

A pulmonary artery endovascular device is under investigation for improving pulmonary artery compliance in PAH and other forms of pulmonary hypertension. This device has been studied so far for temporary use during right heart catheterization, however, development of an implantable permanent device is probably far in the future. Intravascular pulmonary artery denervation is also under investigation.

Conclusion

PAH is a rare but progressive and deadly disease often affecting young women. Accurate diagnosis and risk status assessment are critical before deciding on a treatment plan. Oral, inhaled, and parenteral PAH therapies are available to improve outcome but there is no cure for the disease. New treatments and modalities may further improve outcomes.

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Patient-Focused Treatment Decisions in the Management of Metastatic Melanoma: A Close Look at the Evolving Role of Immunotherapy

Sanjiv S. Agarwala, MD

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

Summary

The first-line treatment of metastatic melanoma has moved away from chemotherapy and is now exclusively immunotherapy or targeted therapy. Both have shown benefits in this setting. Future evolution of treatment may be combined immunotherapy and targeted therapy.

Key Points

- Checkpoint immunotherapy as a single agent or combined immunotherapy are options for all patients with metastatic melanoma.
- Patients with BRAF-mutated tumors also have targeted therapy as an option.
- Triple therapy is a possibility for BRAF-mutated tumors but it has not yet been shown to be superior to sequential therapy.
- Comparative clinical trials between immunotherapy and targeted therapy are ongoing.
- A new therapeutic option is available for metastatic uveal melanoma.

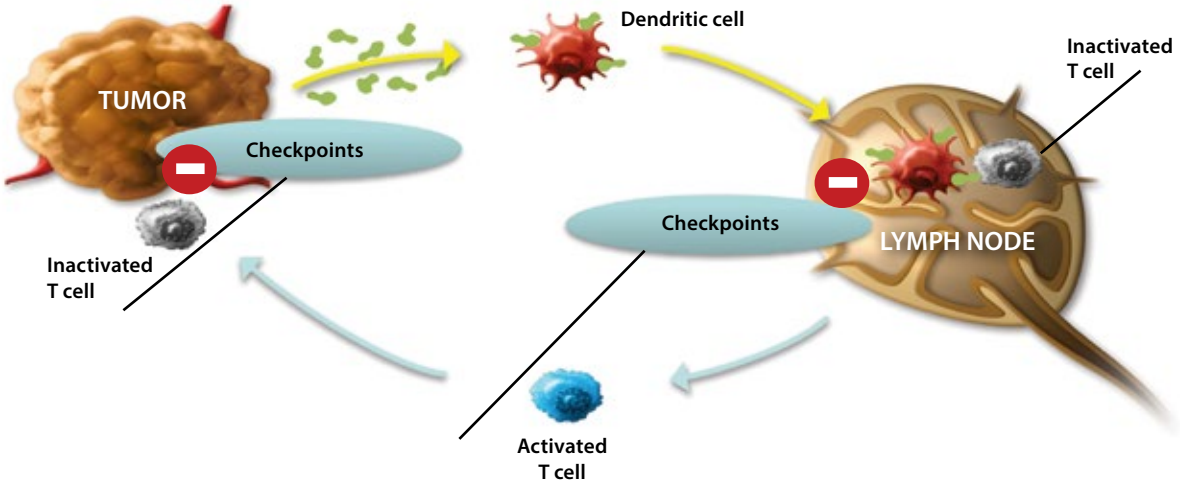
IN 2022 ABOUT 99,780 NEW MELANOMAS will be diagnosed (about 57,180 in men and 42,600 in women) and about 7,650 people are expected to die of melanoma (about 5,080 men and 2,570 women) in the United States (U.S.).[1] Prior to a decade ago, there was no therapy that improved survival in advanced melanoma. Chemotherapy was ineffective and older immunotherapies (interleukin-2, interferon) were only marginally effective, difficult to tolerate, and now are no longer used.

The older immunotherapies showed that melanoma is an immunogenic cancer and thus susceptible to attack from an activated immune system. Immune checkpoints, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), lymphocyte activation gene 3 (LAG-3) and T-cell immunoglobulin and mucin protein 3 (TIM-3) function at different phases in the immune response to regulate the duration and level of the T-cell response.[2] Blocking these immune checkpoints which unleashes the immune system to attack cancer cells has led to a new era of immunotherapy in treating melanoma and many other cancers (Exhibit 1).[2]

Once metastatic and unresectable, the treatment options for melanoma are checkpoint immunotherapy and targeted therapy, if specific genetic mutations are present. Checkpoint immunotherapy used in metastatic melanoma includes the PD-1 inhibitors (nivolumab, pembrolizumab) and nivolumab in combination with the CTLA-4 inhibitor ipilimumab. Targeted therapy includes BRAF (v-Raf murine sarcoma viral oncogene homolog B) and MEK (mitogen-activated protein kinase) inhibitor combinations. An up-and-coming treatment is a triple combination of BRAF/MEK/PD-1 inhibitors.

Ipilimumab was the first checkpoint inhibitor studied in melanoma and completely changed the treatment landscape. The long-term durability of response with ipilimumab was shown in long-term follow-up data from the Phase II and III trials of ipilimumab monotherapy. Among 1,861 patients, median overall survival (OS) was 11.4 months, which included 254 patients with at least three years of survival follow-up. The survival curve began to plateau around year three, with follow-up of up to 10 years.[3] Ipilimumab monotherapy became the standard of care for advanced melanoma in 2011.

Exhibit 1: The New Immunotherapy Era of Checkpoint Inhibitors[2]



CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1;
LAG-3 = lymphocyte activation gene 3; TIM-3 = T-cell immunoglobulin and mucin protein 3

Pembrolizumab (PD-1) was compared to ipilimumab (CTLA-4) in the KEYNOTE-006 trial.[4] In the final survival analysis, median OS was not reached in either pembrolizumab group (every 2 weeks or every 3 weeks) and was 16.0 months with ipilimumab (p = 0.0009 and p = 0.0008). The 24-month overall survival rate was 55 percent in the two-week group, 55 percent in the three-week group, and 43 percent in the ipilimumab group. After a median follow-up of 57.7 months in surviving patients, median OS was 32.7. months in the combined pembrolizumab groups and 15.9 months in the ipilimumab group (p = 0·00049).[5] Based on improved OS over ipilimumab, PD-1 inhibitors have replaced ipilimumab monotherapy as recommended first-line therapy for metastatic melanoma. The use of checkpoint inhibitors may be the reason for a 7 percent per year decline in the overall melanoma death rate between 2013 and 2017 in people between the ages of 20 and 64.[6]

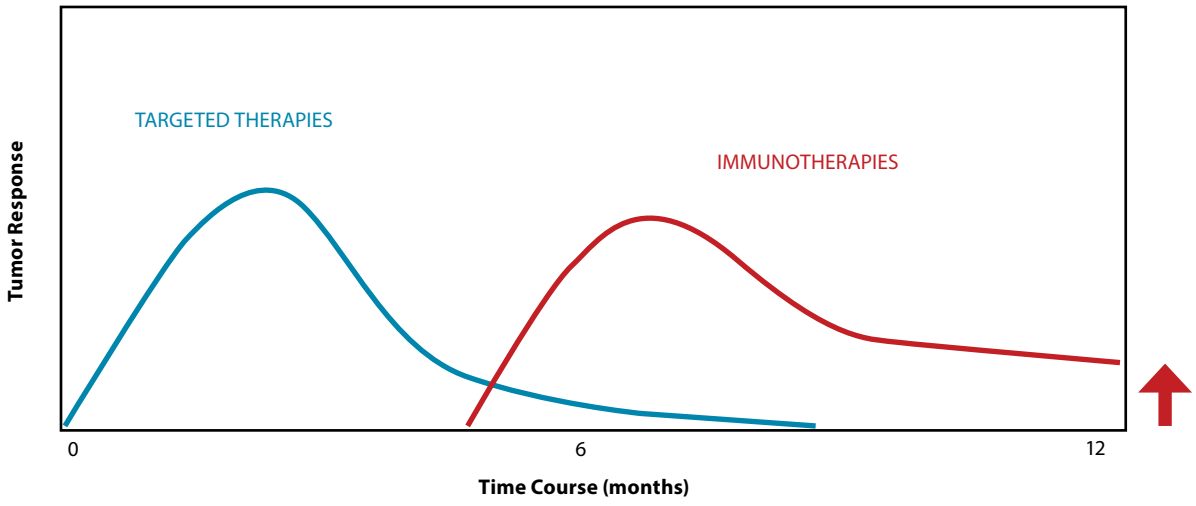
Ipilimumab is now more typically given with nivolumab. The combination improved five-year survival better than ipilimumab or nivolumab alone; OS at five years was 52 percent in the nivolumab-plus-ipilimumab group and 44 percent in the nivolumab group, as compared with 26 percent in the ipilimumab group.[7] Additionally, a higher percentage of patients who received the combination were alive and treatment-free at 6½ years than with nivolumab or ipilimumab monotherapy (77% versus 69% versus 43%).

Thus, clinicians have to make a choice between PD-1 immunotherapy alone or the PD-1/CTLA-4 combination based on efficacy and toxicity. The combination is more effective in improving OS over nivolumab monotherapy but has not been directly compared to pembrolizumab monotherapy. The substantial difference between monotherapy and combination immunotherapy is toxicity. By taking the brakes off of two checkpoint inhibitors, the PD-1/CTLA-4 combination causes a higher rate of immune-related adverse events (irAEs). These irAEs occur earlier than with PD-1 inhibition alone and last longer. Combination therapy is a better choice for those patients in relatively good health who are able to withstand the increased risk of an irAE.

BRAF mutation, primarily V600, is present in approximately 50 percent of melanomas and leads to increased cell proliferation and survival. Previously those with BRAF mutation were treated with a BRAF inhibitor but the effectiveness of this approach is short lived because of resistance development. Dual BRAF and MEK inhibition is associated with high response rates, improves progression-free survival (PFS), and improves OS compared to single agent therapy and has replaced BRAF inhibition monotherapy.[8-10] Dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib are the three combinations approved in the U.S.

If a patient with metastatic melanoma does not have a BRAF mutation, treatment selection would be either monotherapy with pembrolizumab or combination therapy of nivolumab/ipilimumab. If BRAF mutation is present, then a choice must be

Exhibit 2: Antitumoral Response: Targeted Therapies versus Immunotherapies (CTLA-4 antibodies)



made between targeted therapy and immunotherapy. Immunotherapy is effective in BRAF-mutated disease but because there are no direct comparison data, as yet it is not known which is the better option nor the optimal sequencing of targeted therapy and immunotherapy. Real-world data from the Canadian Melanoma Research Network failed to establish any optimal systemic therapy sequencing in advanced BRAF-mutation melanoma patients.[11] Multivariable Cox analysis suggested no OS differences between those who received first-line immunotherapy or targeted therapy. Retrospective analyses of clinical data suggest that progression on targeted therapy is associated with inferior responses to subsequent immunotherapy and that any second-line therapy results in inferior outcomes versus the same therapy in the first-line setting.[12] There are several ongoing trials evaluating targeted therapy compared to nivolumab/ipilimumab. Preliminary finding from one trial showed that two- and three-year OS as well as total PFS rates are higher in the treatment sequences of immunotherapy until progression – then targeted therapy for eight weeks – then immunotherapy until progression – then targeted therapy.[13]

Another option instead of sequencing immunotherapy and targeted therapy is upfront combination of both approaches. As shown in Exhibit 2, targeted therapy has an earlier impact but resistance develops quickly, whereas immunotherapy takes longer to start working but provides longer lasting efficacy. The hope of using both approaches simultaneously is that there will be early tumor response and a higher survival rate long-term.

IMspire150 was a trial studying an initial cycle of vemurafenib/cobimetinib followed by atezolizumab, a programmed death ligand one (PD-L1) inhibitor, or placebo in combination with vemurafenib/cobimetinib. At a median follow-up of 18.9 months, PFS was significantly prolonged with atezolizumab/vemurafenib/cobimetinib versus placebo/vemurafenib/cobimetinib (15.1 versus 10.6 months; $p = 0{\cdot}025$).[14] Final-survival data from this trial have not yet been published but immature survival data presented at an American Association for Cancer Research meeting in 2020 showed benefit on median OS (28.8 months versus 25.1 months) and 24 month survival (60.4% versus 53.1%).[15] The National Comprehensive Cancer Network (NCCN) Guidelines for cutaneous melanoma list this triple combination as other recommended regimen. The guidelines note that final-survival data have not yet been published and the regimen results in a high rate of adverse events.[16]

Central nervous system (CNS) metastases are an unmet clinical need in melanoma. Fifty percent of those with advanced melanoma will develop CNS metastases and the survival rate in these patients is poor. The incidence of CNS metastases has been improving as efficacy of systemic therapy has increased. Response to immunotherapy and targeted agents in the CNS is lower than what is seen in non-CNS disease. Ipilimumab/nivolumab has produced the best responses in the available studies but targeted therapy is an option in those with BRAF mutation.

Uveal melanoma has a distinct biology from

cutaneous melanoma. In the past there has been no standard treatment once it was metastatic and OS was less than 12 months. A newly-approved agent, tebentafusp, is a bispecific gp100 peptide-HLA-directed CD3 T cell engager indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. In vitro, tebentafusp binds to HLA-A*02:01-positive uveal melanoma cells and activates polyclonal T cells to release inflammatory cytokines and cytolytic proteins, which results in direct lysis of uveal melanoma tumor cells. It produces a six-month improvement in median OS in metastatic uveal melanoma as first-line therapy compared to pembrolizumab, ipilimumab, or dacarbazine and is a category 1 recommendation for first-line use in the NCCN Guidelines.[17,18]

Numerous other agents and combinations are under study for melanoma. For example, agents targeting LAG-3 are being studied in combination with PD-1 inhibition. Agents blocking TIM-3 are also under study. Due to adaptive resistance, the expression of TIM-3 is up-regulated in PD-1/PD-L1 blocking therapy resistant tumors.[19] Therefore, blocking TIM-3 may restore effectiveness of PD-1/PD-L1 blocking therapy. Talimogene laherparepvec (T-VEC), an FDA-approved intralesional oncolytic virus immunotherapy, is being studied in combination with pembrolizumab.

Conclusion

Immunotherapy is an option for all patients with metastatic melanoma as a single agent or in combination. Targeted therapy is an option for those with BRAF-mutated tumors. Triple therapy for BRAF-mutated tumors is an approved option but the data are controversial. For now, the choice between immunotherapy and targeted therapy is still a clinical decision but randomized comparative clinical trial data should be available soon.

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