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New Medicare Program Set to Expand Access to Hospice

BY LOLA BUTCHER

Some advanced cancer patients will not have to choose between curative therapy and hospice care after the Centers for Medicare & Medicaid Services (CMS) launches the Medicare Care Choices Model on January 1.

Care Choices is a five-year program in which CMS will explore whether certain Medicare patients with terminal illnesses would be well served by the opportunity to receive hospice services while they are also receiving chemotherapy or other treatment.

Leanne Burrack, RN, Executive Director of Hospice for UnityPoint at Home in three Midwestern states, said she believes the program will make it easier for patients to accept the hospice services that could make their lives easier as their disease progresses.

"They don't have to let go of one rope to grab onto another," she said. "They can hold onto both ropes until they are comfortable."

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Prostate Cancer: Long-Term Anti-Androgens Added to Salvage Radiation Extend Survival

BY ROBERT H. CARLSON

SAN ANTONIO—Salvage radiotherapy plus 24 months of androgen blockage with bicalutamide, when compared with radiotherapy alone, extended long-term overall survival and reduced death from prostate cancer without adding significantly to radiation toxicity in the placebo-controlled Phase III NRG Oncology/RTOG 9601 trial. While trial planning began 20 years ago and the trial was activated in 1998, the findings are still relevant to patient care today.

That was the conclusion of the researchers and the Discussant here at the American Society for Radiation Oncology Annual Meeting, where the data were presented in the plenary session (***Abstract LBA5***).

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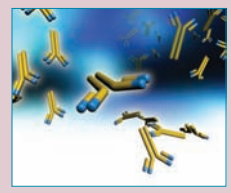
PERIODICALS

Multiple Myeloma: Excitement about Monoclonal Antibodies

BY MARK L. FUERST

NEW YORK—The best treatment for young, fit, transplant-ineligible multiple myeloma patients is three, not four drugs, but the incorporation of new monoclonal antibodies into four-drug regimens has myeloma experts talking about a potential cure, according to experts at the Lymphoma & Myeloma International Conference here.



For such patients, use of four drugs has not shown any additional benefit over the current treatment, said Antonio Palumbo, MD, Chief of the Myeloma Unit, at the University of Torino in Italy. "The only advance of four drugs plus maintenance is mainly for continuous therapy. Continuous therapy improves progression-free survival and overall survival and maximizes benefit. But we never achieve eradication of myeloma. Therefore, complete response and continuous therapy are quite essential."

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New Approvals

FDA

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MAb COMBINATIONS CALLED 'R-CHOP' FOR MYELOMA

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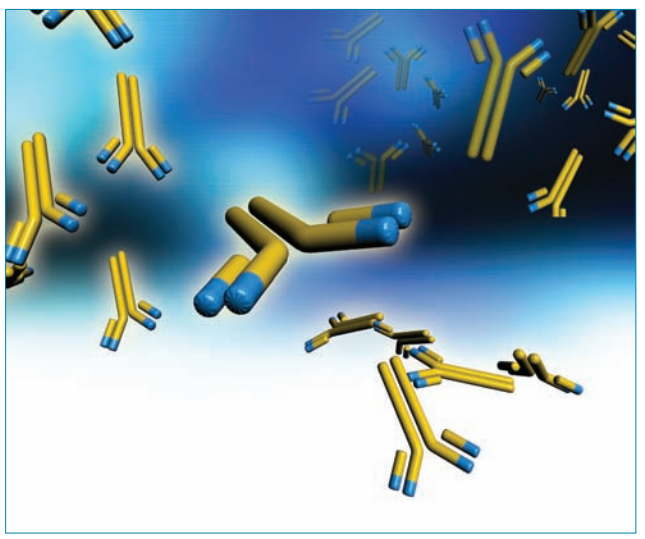
The future of four-drug regimens has brightened with the introduction of monoclonal antibodies in myeloma therapy, he continued. Studies are under way adding the investigational human IgG1k monoclonal antibody daratumumab to bortezomib-thalidomide-dexamethasone or to bor-te-zomib-melphalan-prednisone. Also, the anti-CD38 monoclonal antibody isatuximab has been added to bortezomib-cyclophosphamide-dexamethasone.

"Monoclonal antibodies may make four drugs into R-CHOP for myeloma," Palumbo said, referring to the combination of the anti-CD20 monoclonal antibody rituximab along with cytotoxic therapies, which revolutionized the treatment of B-cell lymphomas.



In an interview, Congress Chair Morton Coleman, MD, Director of the Center for Lymphoma and Myeloma at New York-Presbyterian Hospital/Weill Cornell Medical College, agreed: "We are looking for an R-CHOP-like therapy in myeloma. If we use monoclonal antibodies in combination with second-or third-generation regimens, with or without transplant, we could possibly cure myeloma patients. The next step to a cure is minimal residual disease negativity. With combinations of new modalities, we can start to talk about a cure.

"Young, fit myeloma patients show no benefit from four drugs. What you gain in efficacy you lose in toxicity," Coleman continued. "However, with monoclonal antibodies, there may be a role for a fourth drug."

The Phase II EVOLUTION study compared a four-drug regimen versus two three-drug regimens in young, previously untreated multiple myeloma patients. The regimens included bortezomib-dexamethasone-cyclophosphamide-lenalidomide versus bortezomib-dexamethasone-cyclophosphamide versus bortezomib-lenalidomide-dexamethasone. All regimens were highly active and well tolerated, but the four drugs together increased hematologic toxicity.

"We lose the potential benefit of four drugs. The increase in hematologic toxicity does not translate into clinical benefit," Palumbo said.

Another four-drug versus three-drug study compared the combination of bortezomib-dexamethasone-cyclophosphamide-thalidomide with bortezomib-dexamethasone-thalidomide, and also found higher toxicity with the four-drug regimen.

No matter what combination clinicians choose among the many options, early intervention is essential, Palumbo emphasized. "Time makes the disease more resistant with increasing genetic and epigenetic abnormalities. Treat early for better outcomes."

He noted that for sensitive disease the complete response rate is 56 percent, with a five-year progression-free survival rate of 67 percent and an overall survival rate of 73 percent if patients are treated with a dose-intensive regimen. For resistant disease, the complete response rate is two percent, median progression-free survival is five months, and overall survival is nine months.

Dose-intense treatment with new agents leads to good outcomes in good-risk patients, but not in high-risk patients, Palumbo said, adding that a complete response predicts good outcomes, but patients with resistant disease may not achieve a complete response.

Three Drugs for Elderly Fit Patients

For elderly fit patients, three drugs is clearly the standard. Palumbo recommended a combination of bortezomib and chemotherapy, such as cyclophosphamide and doxorubicin. For patients with extramedullary disease, take into consideration doxorubicin, he said, adding that lenalidomide may lead to better efficacy and less peripheral neuropathy than thalidomide does.

A combination of bortezomib-melphalan-prednisone is the current standard of care in Europe, he said. These three drugs lead to a 52 percent reduction in risk of progression and 36 percent reduction in risk of death. "This is the best available combination of proteasome inhibitors and immunomodulatory drugs [IMiDs]."

In newly diagnosed transplant-eligible multiple myeloma, cyclophosphamide-bortezomib-dexamethasone is "a less expensive alternative with similar effectiveness, but patients achieve a lower CR rate," Palumbo said.

The second-generation proteasome inhibitor carfilzomib added to lenalidomide plus dexamethasone may be effective, but this combination leads to many adverse events and "is too strong," he said. The addition of cyclophosphamide to carfilzomib and dexamethasone is another possibility.

The proteasome inhibitor ixazomib plus lenalidomide-dexamethasone appears to have an effectiveness similar to that of the bortezomib combinations with the advantage of oral administration.

"There is no major difference in combinations with proteasome inhibitors and an IMiD or cyclophosphamide as an alternative," he said.

Two Drugs for Elderly Frail Patients

For elderly frail patients, who comprise 40 percent of the myeloma population, two-drug combinations are best. "This is the most relevant population we see in our offices. With the new treatment algorithm for elderly multiple myeloma, age and comorbid cognitive and physical conditions are all relevant issues. Age 75 does not necessarily make a patient frail."

In the FIRST trial, the combination of two drugs, lenalidomide and dexamethasone, was compared with melphalan-prednisone-thalidomide and with continuous therapy with the pair of drugs. "Two drugs were best. Lenalidomide plus dexamethasone is feasible and has a friendly effect," he said. "The time to next therapy was about three years with continuous therapy. This allows the patient to keep going."

Palumbo noted that "myeloma increases slowly. Two drugs allow these patients to gain nine to 10 months in progression-free survival compared with typical PFS rates. The difference between two or three drugs is not important. For the frail patient with comorbidities who is older than age 80, a two-drug combination should not be dismissed. But a three-drug combination does not provide any additional benefit."

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"With combinations of new modalities, we can start to talk about a cure for myeloma."

Advanced CTCL: Include HSCT as an Option

BY SARAH DIGIULIO

Hematopoietic stem cell transplant (HSCT) should be included as an option for patients with advanced cutaneous T-cell lymphoma—specifically mycosis fungoides and Sézary syndrome. That is the message from Christiane Querfeld, MD, PhD, Director of the Cutaneous Lymphoma Program and Assistant Professor of Dermatology and Dermatopathology at City of Hope Cancer Center & Beckman Research Institute and lead author of a recent review article on the topic.

As she explains in the article (***Dermatologic Clinics 2015;33:807-818***), because there is no cure and none of the standard regimens or investigational regimens have shown a sustained response to treatment, allogeneic transplant has the potential to cure patients with these diseases.

She and her colleagues (first coauthors are Pooja Virmani, MBBS, MD, and Jasmine Zain, MD) review the current data, which has to date been minimal, on conditioning regimens, treatment-related complications, and outcomes for such patients who do undergo HSCT.

The article concludes that for patients with advanced-stage mycosis fungoides (stages IIB to IV) with relapsed or refractory disease or for aggressive CTCL subtypes such as Sézary syndrome, allogeneic HSCT has been shown to result in complete clearance of skin lesions, blood involvement, and other evidence of disease, with some patients achieving long-term remission.

No Clear Guidelines

But, a big challenge for using HSCT for these patients is that there are no clear guidelines to select appropriate patients for stem cell transplant, Querfeld added in an email message.

> "A big challenge for using HSCT for these patients is that there are no clear guidelines to select appropriate patients."

The authors also note that the use of genetic profiling and gene sequencing is likely to allow better prognostic characterization of these tumors and may allow better selection of patients who require transplant for disease control. In addition, dedicated transplant protocols should be developed in multicenter trials to address the needs of these patients with CTCL with improved conditioning regimens and supportive care measures. The increasing number of targeted agents for CTCL, HDAC, and checkpoint inhibitors in particular, should be incorporated into transplant protocols—either in conditioning regimens or as maintenance strategies, the team said.

More Key Conclusions

Other conclusions:

- There is no consensus about the degree of remission needed before transplant for a successful outcome;
- Both related and unrelated matched donors have been used, and there are now supporting data using cord blood as a source of stem cells;
- Although there is still no consensus on conditioning regimens, remissions have been achieved using reduced-intensity approaches, even in patients with advanced and refractory disease, indicating that intense conditioning may not be required for response;
- Total skin electron-beam therapy before transplant may be associated with improved skin control;
- Relapses still occur after allogeneic transplants, but have been treated successfully with adjustments of immunesuppression, donor lymphocyte infusion, or skin-directed treatments; and
- The use of allogeneic stem cell transplant is associated with a higher incidence of complications, including graft-versus-host disease, infections, and death.

MYELOMA

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> "Each year we see improvements in myeloma care. To get to MRD negativity, we will need to use new modalities, such as monoclonal antibodies, in combinations."

A Phase II study in newly diagnosed elderly multiple myeloma patients is now comparing ixazomib plus dexamethasone or ixazomib in three-drug combinations with dexamethasone plus cyclophosphamide, bendamustine or thalidomide, he said.

In conclusion, Palumbo said: "Use a three-drug combination for fit patients, such as induction with bortezomib-cyclophosphamide-dexamethasone or bortezomib-melphalan-prednisone or bortezomib-lenalidomide-dexamethasone for nine to 12 cycles, followed by maintenance with lenalidomide-bortezomib for two years or until disease progression. In frail patients, use induction with two drugs followed by maintenance, such as lenalidomide-dexamethasone, then lenalidomide, bortezomib-dexamethasone, then bortezomib or thalidomide-dexamethasone, and then thalidomide.

'Induction, then Consolidation'

"We have learned from the transplant setting to give induction then consolidation," he continued. "For induction, use two drugs, such as an IMiD or proteasome inhibitor plus dexamethasone for four cycles to reduce toxicities. For consolidation, use three drugs, such as a proteasome inhibitor and dexamethasone plus cyclophosphamide or an IMiD for six to nine cycles to improve efficacy. For maintenance, use a proteasome inhibitor or an IMiD to prolong remission."

If patients are in a grey zone, "use two drugs, not three drugs. Most toxicity occurs during the first few courses of therapy. Use two drugs for three or four courses, and if this is tolerated but not effective enough, add in a third drug," said Palumbo, stressing that maintenance is a must for all patients.

The key, he said, is gentle induction, consolidation, and then maintenance. Continuous therapy in low doses helps keep patients on therapy for the required time, he noted.

Coleman agreed that the standard of care in young, fit myeloma patients is three drugs. "In the U.S., we use proteasome inhibitors, IMiDs, and steroids. The EVOLUTION trial showed that bortezomib plus cytotoxic therapy is almost as good.

"Among community oncologists, bortezomib-lenalidomide-dexamethasone is the most common combination," he continued. "Carfilzomib-lenalidomide-dexamethasone seems to do much better, but there are toxicity issues, such as cardiorespiratory problems, which have to do with the amount of fluid given." He said he believes that given properly, the carfilzomib combination "probably is superior."

Coleman said he thinks that daratumumab should be able to be readily adapted into community practice. "I have seen great responses with daratumumab, which works by itself and in combinations."

FDA Approval

Daratumumab received FDA approval less than a month after the conclusion of the meeting—approved for intravenous infusion for patients who have received at least three prior therapies. The approval is the first for a monoclonal antibody for multiple myeloma.

Cycling Inhibitors

Cycling inhibitors, such as ibrutinib, may also be applicable to myeloma patients. "Right now, the dosage is high, but data suggest that these drugs will work," he said. They appear to work on stromal cells and may interfere with myeloma cell adhesion.

"Each year we see improvements in myeloma care. To get to MRD negativity, we will need to use new modalities, such as monoclonal antibodies, in combinations."