Myeloma: Should Complete Remission, However Strictly Defined, Be the Goal for All Patients?

BY MARK FUERST

NEW YORK—Whether or not every patient with multiple myeloma needs to be "pushed" into a strict complete remission (CR) was debated here at the Lymphoma and Myeloma meeting. Considering the issue were C. Ola Landgren, MD, Chief of the Myeloma Service at Memorial Sloan Kettering Cancer Center; and Joseph Mikhael, MD, Associate Professor of Medicine in Hematology/Oncology, at the Mayo Clinic in Arizona,

Three groups of multiple myeloma patients—those with monoclonal gammopathy of undetermined significance (MGUS)-like myeloma, those with indolent clinical myeloma, and elderly patients—do not necessarily need to achieve CR, according to the consensus of the audience of approximately 400, who were polled after the debate, two-thirds of whom consisted of physicians who see one to five patients a week, according to statistics from the meeting.

C. Ola Landgren: Yes, a Complete Response Should be the Goal for All Patients

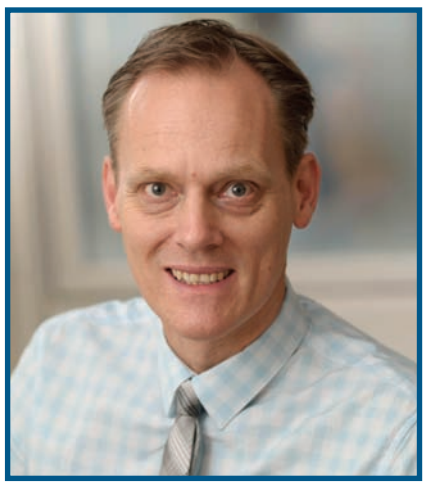
Complete remission, however strictly defined, should be the goal for everyone, Landgren said. "Good clinical response is important, and newer myeloma drugs provide better clinical responses. More patients are reaching deeper responses. This matters for patients. Clinical response to therapy impacts progression-free survival as well as overall survival."

The quality of response also matters, and myeloma genetics and minimal residual disease (MRD) status have an impact on overall survival (OS). "Why stop at CR when you know you are not done?" he asked. "MRD serves as a prognostic factor. Patients who achieve stringent CR have better PFS and OS than CR. Among CR patients, flow cytometry MRD negativity impacts survival and leads to a better clinical outcome.

"We don't have an established cure," Landgren continued. "Treating myeloma is not a snap shot—it's more of a marathon."

There is already literature to support treating patients to CR. "We are already doing it," he said. "A number of myeloma MRD studies have been published associated with clinical outcomes, and many papers are being submitted to journals that replicate these findings."

In conclusion, Landgren said: "We are seeing deeper responses in more patients. Deeper responses equal better survival. Deeper responses are therefore better. MRD is the next step forward."



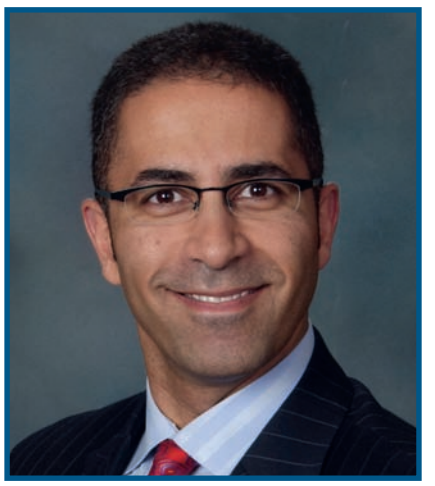
C. OLA LANDGREN, MD, PHD: "We are seeing deeper responses in more patients. Deeper responses equal better survival. Deeper responses are therefore better. MRD is the next step forward."

Joseph Mikhael: No, Not All Patients Need to Achieve CR

Taking the opposing view, Mikhael said that he didn't think that all myeloma patients need to achieve a strict complete response: "In general, people do better with deep response. When people respond, we are happy. But we do not need to push every patient to move forward to get into strict CR."

As background, Mikhael noted that therapy for myeloma has rapidly evolved and that there is now more intense regimens and prolonged therapies.

"This has resulted in deeper and more durable responses, and translates into doubling—if not tripling—of median OS. But is it really all about depth of response? It is much more than CR."



JOSEPH R. MIKHAEL, MD: "Of course, CR is good, and should be the goal for most patients. However, there remains a subset of patients with more indolent myeloma who do not require CR for long-term survival."

He explained his thesis as "of course, CR is good, and should be the goal for most patients. However, there remains a subset of patients with more indolent myeloma who do not require CR for long-term survival."

Identifying those patients is critical. Clinicians need to modify their expectations, not over-treat, and estimate prognosis. "Choose the right weapon. Be careful not to over-treat," he said.

> "The choices clinicians have to treat a multiple myeloma patient is similar to that of a general practitioner who sees a patient with high cholesterol and high blood pressure levels. The doctor has to deal with it, or not. Myeloma patients need CR for better long-term outcome in terms of OS. I don't buy the argument that we should not treat because it's harmful."

He urged those listening to recall the heterogeneity of myeloma, noting the biological and clinical differences of the disease: "Myeloma, based on definition, may indeed be the most common malignancy worldwide. We surely cannot treat all patients in the same way. We need to individualize therapy," said Mikhael, emphasizing the importance of risk stratification.

Over the last three decades, the definition of acute leukemia has changed from what it looks like to the use of

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cytogenetics. "Multiple myeloma sub-classifications have become more sophisticated over time as well," he said.

The introduction of novel therapies for multiple myeloma has had an impact on survival. From 2012 to 2013, more than half of multiple myeloma patients over age 65 survived for five years, compared with less than a third from 2001 to 2005, he pointed out.

Updated Mayo stratification of myeloma and risk-adapted therapy (mSMART) consensus guidelines, published in 2013, further define the risks of multiple myeloma patients (***Mikhael JR et al: Mayo Clinic Proceedings 2013;88:360-376***).

> "Biology is teaching us that we can predict certain individuals who do not require CR, using cytogenetics, response to treatment, and toxicity. I'm open to exclude those as not having CR. But sometimes, we have to modify our expectations."

According to the classification, 20 percent of these patients are high-risk, defined by FISH del 17p, t(14;16), and t(14;20) and a gene-expression profile with a high-risk signature. Another 20 percent of patients are considered to be intermediate-risk with FISH t(4;14), cytogenetic deletion 13 or hypodiploidy, and a plasma cell labeling index of more than three percent. Approximately 60 percent of patients are at standard risk, including those who are hyperdiploid and with translocations t(11;14) and t(6;14).

At the meeting, Mikhael defined three groups of patients who he believes do not need to achieve a complete response:

- Group 1 are patients with those with MGUS-like myeloma—Genotypically, they have hyperdiploid multiple myeloma, possibly some t(11:14), and a gene-expression profile defined by MGUS-like multiple myeloma;
- Group 2 are patients with indolent clinical myeloma, phenotypically, with prolonged MGUS or smoldering myeloma; and
- Group 3 are elderly patients who are more frail and sensitive to toxicity and therefore the achievement of a CR may be more toxic.

"Group 1 patients have a gene-expression signature of benign monoclonal gammopathy evident in multiple myeloma that is linked to good prognosis," he said. "They are less likely to go into CR. They show improved survival over non-MGUS-like multiple myeloma. The majority of them who are long-term survivors are MGUS-like and do well."

He noted that studies show that CR in myeloma extends survival without, but not with, a history of prior MGUS or smoldering disease. "Long-term survival is possible in patients post-transplant. Patients with 'evolved' multiple myeloma prior to MGUS or smoldering myeloma have lower CR with Total Therapy 2 treatments. CR is critical in this non-evolved group."

In Group 2 patients, there is long-term prognostic significance of response in multiple myeloma after stem cell transplantation. There are no differences in outcomes in patients who achieve a near CR, a very good partial response, or partial response. Those who achieve CR live much longer than those with lesser responses—"These patients do not require CR to have 20-year survival," he said.

"For Group 3 patients, the goal of achieving CR can often lead to more intense therapies. Dose reduction in elderly patients remains critical. Depth of response may take longer and may not be as deep. There is discordance between CR and survival in this group. CR does

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not always predict for PFS or OS," he continued.

"Lower CR may mean better survival. Depth does not always coordinate with response.

"So what does this mean for my clinic next week? CR is a noble goal and is generally sought after, especially in high-risk disease. However, it is not the goal in all, especially in those three groups of patients."

If a patient meets the criteria for one of these groups, Mikhael said, "be careful not to over-treat, and anticipate prolonged survival in groups 1 and 2. Remember that CR does not equal CR in standard versus high-risk patients, and response is always depth plus duration."

Still, he said, "I agree with Ola that in the highest-risk patient, we really want a CR. We need to get them into CR and keep them there. In high-risk patients who start to relapse, don't wait four or five months to treat. They are prone to turn into a bonfire. These patients tend to have more active disease. One agent may not be enough."

He noted that novel agents lead to less cytopenia and neuropathy.

"Biology is teaching us that we can predict certain individuals who do not require CR, using cytogenetics, response to treatment, and toxicity. I'm open to exclude those as not having CR. But sometimes, we have to modify our expectations," Mikhael said.

Q&A

During the question-and-answer period, an audience member asked if transplant-ineligible patients need to reach MRD negativity or CR.

Landgren answered that transplant ineligibility should not be a discriminator for treatment, and reiterated that the goal for all patients should be complete response. "If a patient does not reach CR after several therapies, do not over-treat. With new, novel drug combinations, the majority of patients go into CR."

Mikhael noted the need to match biology. "Patients who return to the MGUS state—that is, have clonal evolution—often have multiple clones. Quite often the indolent clone remains. Be careful about evaluation. The reality is if we treat these patients aggressively, with two to three rescues and still have a remaining myeloma spike, they probably have slow, indolent clones and there is no point trying to remove it."

James R. Berenson, MD, President and CEO of the Institute for Myeloma & Bone Cancer Research in California, commented: "My longest surviving patient has had multiple myeloma for 31 years with active disease the whole time. We would like to get CR. We have 20 options now."

Landgren likened the choices clinicians have to treat a multiple myeloma patient with that of a general practitioner who sees a patient with high cholesterol and high blood pressure levels. "The doctor has to deal with it, or not. Myeloma patients need CR for better long-term outcome in terms of OS. I don't buy the argument that we should not treat because it's harmful," he said.

In a post-debate survey, three-quarters of the audience voted no in answer to the debate question, which was an increase from slightly more than half before the debate. The percentage of "yes" voters dropped from one-third to 15 percent, making Mikhael the clear winner of the debate.