Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 10% of all hematologic cancer cases. It is estimated that 26,850 new cases will be diagnosed and 11,240 deaths will occur in the United States in 2015. The introduction of new agents with substantial activity has improved outcomes and allowed patients to experience longer periods of remission. Both novel proteasome inhibitors and immunomodulatory agents have effectively transformed the standard treatment for patients with newly diagnosed and relapsed/refractory MM. Although various maintenance strategies have been incorporated into current treatment algorithms, little is known about the adoption of these therapeutic approaches in clinical practice. The current challenge facing the oncology community is identifying those patients who will obtain the greatest benefit from a specific regimen while incurring the least toxicity.

In January 2014 more than 6,500 practicing oncologists from Research To Practice’s proprietary email database were invited to complete an extensive case-based survey focused in part on the management of MM. This CME endeavor documents the self-reported practice patterns of 101 general medical oncologists who elected to participate. The activity also offers clinical investigator perspectives on these findings in addition to their preferred approaches to the same scenarios examined. This information is presented in an effort to allow practicing medical oncologists to compare and contrast their own practice patterns to those of their peers and hematologic oncology experts and modify them accordingly.

LEARNING OBJECTIVES

- Compare and contrast induction and maintenance treatment strategies used by general oncologists and cancer clinical investigators, and apply this knowledge to individualize therapy for patients with MM.
- Evaluate the effects of patient age and risk status on the selection of induction and maintenance therapy for patients with MM.
- Determine the optimal duration of maintenance therapy for transplant-eligible patients with MM.
- Assess the risk of second primary cancers with the use of maintenance lenalidomide, and use this information to counsel patients with MM.

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independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Division of Medical Oncology
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Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Onyx Pharmaceuticals, an Amgen subsidiary; Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Lilly, Onyx Pharmaceuticals, an Amgen subsidiary; Contracted Research: Celgene Corporation, Onyx Pharmaceuticals, an Amgen subsidiary; Speakers Bureau: Celgene Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals, an Amgen subsidiary.

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Hardware/Software Requirements:
Apple iPad 1, 2 or the New iPad
iBooks 2
iTunes 10.5.3

Last review date: January 2015
Expiration date: January 2016

After completing the post-test, learners may download and review the answers here in order to identify further areas of study. You must be connected to the Internet to access the Post-test answer key using a web browser.
Induction treatment for younger, transplant-eligible patients at standard risk

An otherwise healthy 60-year-old patient presents with fatigue. Workup reveals Hb 9.0 g/dL, normal renal function, an M-spike with an IgG lambda component of 4.9 g/dL and bone marrow consistent with MM (ISS Stage II). Conventional cytogenetics, FISH and skeletal survey are normal. Which induction treatment would you most likely recommend for this patient?

**EDITOR’S COMMENTS**

The first scenario we asked about was a younger patient (age 60) with normal-risk myeloma who is a transplant candidate, and we found that by far the most common choice of induction treatment was RVD (lenalidomide/bortezomib/dexamethasone), the same choice as that of both faculty. Surprisingly, relatively few oncologists chose the other much-discussed triplet regimen, CyBorD (cyclophosphamide/bortezomib/dexamethasone). In spite of the encouraging results in 2 major Phase II trials, the CRD regimen with carfilzomib is not being used, but the Phase III randomized ECOG-E1A11 trial is comparing CRD to RVD.

**SELECT REFERENCES WITH LINKS**


Most patients receive pretransplant induction regimens that include bortezomib, and we were curious — after a landmark study several years ago demonstrated the feasibility of subcutaneous rather than intravenous (IV) bortezomib — whether this approach is used in induction treatment. We found that more than 80% of oncologists and the faculty generally administer bortezomib subcutaneously, mostly on a twice-weekly schedule, although Dr Vij notes that the equivalence in efficacy to IV treatment has been demonstrated only in the relapsed setting. Dr Munshi notes that when a rapid response is needed — for example, in patients with renal failure — IV administration might be preferred initially.


For patients at standard risk, more than 85% of respondents and the faculty use maintenance treatment after autologous stem cell transplant, including for patients with a very good partial or a complete response (CR). The regimen choice is the same for both levels of response, almost always lenalidomide with or without dexamethasone. Dr Vij notes that prior to Phase III maintenance trials, many investigators speculated that patients in post-transplant CR would not benefit, but recent trials have demonstrated benefit in all response subsets. Dr Munshi notes that new techniques to define minimal residual disease may identify patients not requiring maintenance.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complete response</th>
<th>Very good partial response</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>64%</td>
<td>69%</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>RD or Rd</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>RV</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>VD</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>RVD</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**EDITOR’S COMMENTS**


Another critical post-transplant maintenance issue is the duration of therapy, and both faculty treat indefinitely or until disease progression, the same strategy used in the CALGB-100104 trial that demonstrated a survival benefit with lenalidomide maintenance. Our survey indicates that only about half of oncologists use indefinite maintenance, with the others stopping therapy after 1 to 2 years. Several Phase III trials are evaluating limited-duration versus indefinite treatment, including ECOG-E1A11. Dr Munshi notes that studies of defined duration usually demonstrate an increase in relapses from the time treatment is discontinued.


We queried participants about their usual daily dose of lenalidomide maintenance therapy for a younger (60-year-old) otherwise healthy patient with MM who responded to induction therapy and ASCT, what is your usual preferred starting dose?

<table>
<thead>
<tr>
<th>Dose</th>
<th>% of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg</td>
<td>29%</td>
</tr>
<tr>
<td>20 mg</td>
<td>13%</td>
</tr>
<tr>
<td>15 mg</td>
<td>21%</td>
</tr>
<tr>
<td>10 mg</td>
<td>37%</td>
</tr>
</tbody>
</table>

In general, when administering lenalidomide maintenance therapy for a younger (60-year-old) otherwise healthy patient with MM who responded to induction therapy and ASCT, what is your usual preferred starting dose?

We queried participants about their usual daily dose of lenalidomide maintenance, and while Dr Munshi uses 15 mg and Dr Vij 10 mg, a surprising 29% of the oncologists opt for 25 mg. This concerns Dr Vij, who believes that in the post-transplant setting 25 mg often produces cytopenias. CALGB-100104 started with 10 mg and, if that was well tolerated, stepped the dose up to 15 mg, but Dr Vij uses 10 mg because in his experience patients usually end up receiving that dose. Dr Munshi believes that even in patients tolerating 25 mg, toxicities often accumulate with time. He questions patients carefully about fatigue, noting that dose reductions of even 5 mg can have a positive effect on quality of life.

**Select References with Links**


An otherwise healthy 60-year-old patient presents with fatigue. Workup reveals Hb 9.0 g/dL, normal renal function, an M-spike with an IgG lambda component of 4.9 g/dL and bone marrow consistent with MM (ISS Stage II). FISH reveals del(17p), and skeletal survey is normal. Which induction treatment would you most likely recommend for this patient? Which post-transplant maintenance treatment, if any, would you most likely recommend if the patient received your induction treatment of choice, underwent ASCT and achieved a complete response?

<table>
<thead>
<tr>
<th></th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD</td>
<td>57%</td>
<td>None</td>
</tr>
<tr>
<td>CyBorD</td>
<td>14%</td>
<td>Lenalidomide</td>
</tr>
<tr>
<td>VD</td>
<td>10%</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>7%</td>
<td>RV</td>
</tr>
<tr>
<td>RD or Rd</td>
<td>4%</td>
<td>RVD</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>4%</td>
<td>VD</td>
</tr>
<tr>
<td>RV</td>
<td>1%</td>
<td>RD or Rd</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
<td>Second tandem transplant</td>
</tr>
</tbody>
</table>

**EDITOR’S COMMENTS**

We asked about patients with high-risk cytogenetics, specifically 17p deletion, and found induction treatment similar to those for patients at standard risk, the most common regimen being RVD, also used by both faculty. However, the approach to post-transplant maintenance is different, as 39% of oncologists and both faculty incorporate bortezomib, a practice that increased quickly after presentations of the HOVON-65 study, which used bortezomib-based induction and maintenance. Dr Munshi administers RVD maintenance, an approach described in a recent publication by Dr Sagar Lonial in *Leukemia*, and Dr Vij opts for lenalidomide and bortezomib without dexamethasone.

**SELECT REFERENCES WITH LINKS**

One of the most interesting and unexpected findings in this survey related to the use of corticosteroids as part of maintenance therapy. For patients receiving lenalidomide maintenance we found a split in corticosteroid use, with Dr Vij not using this strategy because he questions the rationale for adding the immunosuppressive effect of corticosteroids to an immunomodulatory agent and Dr Munshi adding corticosteroids to lenalidomide, citing a recent Italian trial that demonstrated a progression-free survival benefit with 50-mg prednisone administered 3 times a week, although he uses dexamethasone 10 to 20 mg weekly.

**SELECT REFERENCES WITH LINKS**


A critical and emergent clinical scenario in myeloma management is a patient presenting with the disease in acute renal failure. The 2 most common initial therapies used are CyBorD (the choice of both faculty) and bortezomib/dexamethasone. Dr Vij notes that data from nonrandomized studies suggest that reversal of renal dysfunction within the first few months allows patients to live nearly as long as those who started out with normal renal function, and for this reason he approaches these cases aggressively with a 3-drug regimen.


We asked about up-front treatment for an older, transplant-ineligible patient, in this case aged 77, at standard risk. The 2 most common choices were Rd (also used by both faculty) and RVD, often used at reduced doses as in the “RVD lite” regimen. One surprising finding is that the use of melphalan continues in a small subset of oncologists, a practice likely to change considering the data from the FIRST trial that demonstrated a significant PFS and OS benefit with continuous Rd compared to melphalan/prednisone/thalidomide. Dr Munshi evaluates patients’ frailty and comorbidities in choosing between RVD lite and Rd but leans toward RVD for symptomatic patients to induce a more rapid response.

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**Editor’s Comments**

An otherwise healthy 77-year-old patient presents with fatigue. Workup reveals Hb 9.0 g/dL, normal renal function, an M-spike with an IgG lambda component of 4.9 g/dL and bone marrow consistent with MM (ISS Stage II). **Conventional cytogenetics, FISH and skeletal survey are normal.** The patient is not eligible for transplant. Which induction treatment would you most likely recommend for this patient?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>RD or Rd</td>
<td>30%</td>
</tr>
<tr>
<td>RVD</td>
<td>23%</td>
</tr>
<tr>
<td>VD</td>
<td>13%</td>
</tr>
<tr>
<td>CyBORd</td>
<td>11%</td>
</tr>
<tr>
<td>VMP</td>
<td>7%</td>
</tr>
<tr>
<td>MPR</td>
<td>6%</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>5%</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>5%</td>
</tr>
</tbody>
</table>

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**Select References with Links**


Almost all oncologists administer maintenance treatment for elderly patients, usually (as with the faculty) after maximal response is observed. The FIRST trial used two approaches to Rd, one for a fixed duration of 18 cycles and the other indefinitely, which was the randomization arm with the best results. Dr Vij treats indefinitely, but for older patients receiving bortezomib he generally limits maintenance to 1 year, particularly because of the inconvenience of parenteral administration. Dr Munshi notes that the recent emergence of oral proteasome inhibitors such as ixazomib and oprozomib may dramatically alter the landscape for proteasome maintenance therapy in the future.


In general, when administering lenalidomide maintenance therapy for an older (77-year-old), otherwise healthy patient with MM who responded to front-line therapy but was not eligible for transplant, what is your usual preferred starting dose?

25 mg: 18%
20 mg: 8%
15 mg: 30%
10 mg: 44%

% of respondents

EDITOR’S COMMENTS

We asked about the usual dose of lenalidomide in the maintenance setting for older patients, and although the faculty and most oncologists used 10 or 15 mg, again, about a quarter would use a higher dose. Dr Munshi is concerned about the higher baseline risk of myelodysplastic syndromes in older patients, particularly because patients with myeloma are at greater baseline risk, and he carefully monitors blood counts and discontinues lenalidomide at the first sign of any cytopenias.

SELECT REFERENCES WITH LINKS


We also asked about the approach to treatment for a 77-year-old patient with high-risk cytogenetics, specifically a 17p deletion, and most oncologists and the faculty would cautiously use RVD. Dr Vij notes that preemptive dose reductions may be considered for elderly or frail patients but that the poor short-term outcomes of myeloma in this situation must be balanced against the potential for toxicity.

**Select References with Links**


In general, which thromboprophylaxis, if any, do you recommend for patients with MM who are receiving maintenance therapy with lenalidomide (with or without dexamethasone)?

**Editors' Comments**

A practical question that is particularly relevant in the long-term maintenance setting is that of thromboprophylaxis for patients receiving lenalidomide, and although almost half of the oncologists use standard-dose aspirin, both faculty use a minidose of 81 mg. Dr Munshi administers warfarin or low-molecular-weight heparin to patients at increased risk, including those with a history of deep vein thrombosis and patients who are immobile or very elderly.

**Select References with Links**


When using post-transplant lenalidomide maintenance, how do you counsel a patient about the risk of second primary cancer?

- Evidence suggests a modestly increased risk of both solid and hematologic cancers: 37%
- Evidence suggests a modestly increased risk of hematologic cancers: 27%
- Evidence suggests a modestly increased risk of solid cancers: 1%
- Evidence is conflicting, and it’s not clear if there is an increased risk of either solid or hematologic cancers: 34%
- There is no increase in risk: 1%

**EDITOR’S COMMENTS**

To obtain a broader perspective on how physicians view the complex question of second primary cancers with lenalidomide, we asked what they say to patients in this regard and found that the faculty and most oncologists tell patients that the risk of both solid and hematologic cancers is modestly increased. But about a third of oncologists are not convinced of this association. Both faculty note that when they counsel patients about this modest risk they are careful to explain that it is more than balanced by the antmyeloma effect on disease progression.

**SELECT REFERENCES WITH LINKS**


One of the issues with proteasome inhibitor therapy that is particularly relevant in the longer-term maintenance setting is the potential for herpes zoster reactivation, and we asked about the specific choice of antiviral agent and found that acyclovir rather than valacyclovir was the most common selection by oncologists and the faculty. Dr Vij believes that although these agents are equally effective, valacyclovir has the convenience of once-daily administration, whereas full-dose acyclovir is administered 3 times a day. However, he notes that oncologists are often limited by insurance carriers’ preferences for acyclovir, which is generic and less expensive.

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**Select References with Links**
