ABSTRACT

The management of relapsed/refractory multiple myeloma is based in part on the degree of previous exposure and resistance to commonly used drug classes. For patients with a first relapse, an anti-CD38 antibody-based combination is preferred unless patients have already received these agents, in which case a carfilzomib-based option can be an excellent choice. For patients with more refractory disease, a bispecific antibody is an emerging choice, but CAR T-cell therapy should also be considered for some patients; other options include salvage autologous transplantation, recycling of previous therapies, and selinexor-based therapies. Emerging new classes of drugs in development are poised to broaden the treatment possibilities for relapsed disease.

Globally, cases of multiple myeloma are increasing—an estimated 150,000 Americans are currently living with this malignancy. Fortunately, treatments have become available in the past few years that extend survival, although most patients will experience relapses. Clinicians are tasked with selecting the best treatment options for these progressions from among a growing cascade of regimens. Explaining this treatment landscape at the NCCN 2023 Annual Conference was Natalie S. Callander, MD, Professor of Medicine, University of Wisconsin School of Medicine and Public Health, and Director, Myeloma Clinical Program, Carbone Cancer Center, and member of the NCCN Guidelines Panel for Multiple Myeloma.

Key Concepts in Addressing Relapse

Dr. Callander touched on some key concepts that should be appreciated upon relapse: (1) symptomatic relapse typically requires immediate intervention; (2) high-risk (or functional high-risk) patients require more intensive therapy at every relapse (at least triplets for fit patients); (3) standard-risk patients can sometimes be observed before starting treatment if reevaluation does not reveal extensive or organ-compromising disease; and (4) autologous stem cell transplantation is an option for first relapse if the patient has not previously received one, or is ≥24 months post-transplant if they had previously undergone transplant.

She then discussed reevaluation on relapse, noting that advanced imaging is “critical” and bone marrow biopsy may be helpful. When selecting therapy, a careful review of past medications that were effective and determining whether there are residual side effects is very important. Additionally, the patient’s level of fitness and family support should also be considered.

Early Relapse: After Initial Therapy or Between 2 or 3 Previous Lines of Therapy

On first relapse, many patients will have received lenalidomide or will still be on lenalidomide maintenance. For patients experiencing relapse while on lenalidomide maintenance, there is no real benefit to increasing the dose of this drug as a treatment strategy. The addition of dexamethasone may be helpful for patients who experience very slow biochemical disease progression, but there are better options, Dr. Callander stated. “Particularly, introduction of an anti-CD38 monoclonal antibody in a triplet should be a strong consideration because this can reverse refractoriness,” she said. Triplets approved by the FDA include daratumumab + lenalidomide/dexamethasone; daratumumab or isatuximab + carfilzomib/dexamethasone; and elotuzumab or isatuximab + pomalidomide/dexamethasone.

Numerous phase III trials, including POLLUX,² CASTOR,³ and APOLLO,⁴ have demonstrated high response rates and prolonged progression-free survival (PFS) when daratumumab is added to a standard backbone. These regimens, which are efficacious and usually well tolerated, have become a preferred strategy in the first relapse setting, she said. The antibody isatuximab in combination with either pomalidomide or carfilzomib also showed significant benefit in the phase III ICARIA-MM⁵ and IKEMA⁶ trials, respectively.

For patients with early-relapse disease who were recently exposed to daratumumab, treatment should be with a regimen that does not contain an anti-CD38 antibody. Dr. Callander prefers elotuzumab + pomalidomide/
Management of R/R Multiple Myeloma

dexamethasone, based on data from the phase II ELOQUENT-3 trial,\(^7\) which showed a 46% reduction in the risk of disease progression (\(P=0.008\)) and an overall survival (OS) benefit. “There are also data showing that if you treat a patient with an antibody-based combination at first relapse, you’re not ruining them for a response later on, which is obviously important,” she added.

Other choices recommended by Dr. Callander in the early-relapse setting are pomalidomide/bortezomib/dexamethasone and selinexor in combination with weekly bortezomib + dexamethasone; she advised reducing the dose of selinexor to 40 to 60 mg weekly to improve tolerability. The older regimen of weekly carfilzomib + lenalidomide/dexamethasone is well-tolerated and is a reasonable option if the patient is not on lenalidomide at relapse. Carfilzomib-based triplet regimens can be also a good choice for patients with higher-risk myeloma, and carfilzomib can transitioned to maintenance.

**Treatment Beyond the Third Line**

“Most patients will have become ‘triple-class refractory’ to an immunomodulatory drug, protease inhibitor, and antibody. The tempo of this relapse is critical,” stated Dr. Callander. She noted a few factors to consider: Does this patient need a quick response? How close is a transplant or academic center that might offer cellular therapy? How fit is the patient?

There are several options for patients who have had at least 4 prior therapies (Table 1). She noted that the antibody–drug conjugate belantamab mafodotin-blmf has been voluntarily withdrawn from the market, although some believe it could become available again in the future. “A lot of [clinicians] like selinexor in combination with carfilzomib for later-line therapy, because we think there is the ability to salvage patients who have had treatments such as CAR T-cell therapy,” she said. In a recent study that included patients previously treated with CAR T-cell therapy, a response rate of 78% was reported.\(^8\)

A second autologous transplantation is an option, particularly if the patient had stem cells collected and the posttransplant interval is at least 24 months.\(^4\) Another available option is to “recycle” old therapies: patients who received an anti-CD38 antibody–based combination >6 months ago may experience a response again to the inclusion of such agents. Additionally, older lines of therapy to which the patient experienced a response can be “reshuffled.”

**Era of Immunotherapy and Bispecific Antibodies**

“Myeloma is headed toward immunotherapy in the next few years, in a big way,” Dr. Callander said. These agents include antibody–drug conjugates, CAR T-cell therapy, bispecific T-cell engagers, and naked antibodies, many of which target B-cell maturation antigen (BCMA). Therapeutics with new targets are also in development.

The MajesTEC-1 study evaluated the BCMA-targeting bispecific antibody teclistamab as a single agent in patients with triple-class–refractory disease. The response rate was 63.0%, with 58.8% being very good partial responses or better; median PFS was 11.3 months, and median OS was 18.3 months.\(^9\) Cytokine-release syndrome can occur, as can immune effector cell–associated neurologic syndrome (although less so than with CAR-T therapy and typically during the first couple of doses), which may explain the relatively slow uptake in the community. Dr. Callander expects greater adoption of teclistamab in the near future, along with its use earlier in treatment.

However, teclistamab is but one of many BCMA-targeted bispecific antibodies in development (Table 2). Talquetamab and cevostamab are also bispecific antibodies, but they have novel targets: G protein–coupled receptor family C group 5 (GPRC5D) and FcRH5, respectively. The bispecific antibodies that target BCMA, as a class, carry a risk for infection that mandates close monitoring.

**CAR T-Cell Therapy**

In myeloma, CAR-T therapy targeting BCMA has a useful role in treating patients who can afford a 4- to 6-week delay while the product is manufactured. There are 2

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**Table 1. Options for Patients After ≥4 Prior Therapies**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Patients (n)</th>
<th>ORR</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
<th>CRS, % Any Grade</th>
<th>NT, % Any Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selinexor(^{16})</td>
<td>II</td>
<td>122</td>
<td>26%</td>
<td>3.7</td>
<td>8.6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Belantamab mafodotin(^{17})</td>
<td>II</td>
<td>97</td>
<td>32%</td>
<td>2.8</td>
<td>13.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Idectagatine vicleucel</td>
<td>II</td>
<td>128</td>
<td>73%</td>
<td>8.8</td>
<td>24.8</td>
<td>84</td>
<td>18</td>
</tr>
<tr>
<td>Citabtagatine autoleucel(^{11})</td>
<td>ib/II</td>
<td>97</td>
<td>98%</td>
<td>NR</td>
<td>NR</td>
<td>95</td>
<td>22</td>
</tr>
<tr>
<td>Teclistamab(^{9})</td>
<td>ib/II</td>
<td>165</td>
<td>63%</td>
<td>11.3</td>
<td>NR</td>
<td>72.1</td>
<td>14.5</td>
</tr>
</tbody>
</table>

Abbreviations: CRS, cytokine-release syndrome; NA, not applicable; NR, no response; NT, ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
commercially available CAR-T products: idecabtagene vicleucel and ciltacabtagene autoleucel.

Approval for idecabtagene vicleucel was based on the KarMMa trial, where the response rate was 73%, median PFS was 12 months, and 2-year OS was 51%. Approval of ciltacabtagene autoleucel was based on CARTITUDE-1, where the response rate was 97.9%, median PFS was 60 months, and 27-month OS was 70.4%. Real-world experience has shown that response and PFS rates in unselected patients are comparable to those achieved in clinical trials.

“You must have a patient whose myeloma is reasonably well controlled . . . I think most centers, including ours, are realizing there are some patients who cannot consider this therapy because they are not stable enough to do so,” Dr. Callander said. She added that availability is also an issue at most centers and these therapies appear to be more difficult to access for patients living far from an academic center. “Hopefully, some of these access issues will be resolved in the near future.”

Of note, CAR T-cell therapy is not curative in myeloma, and patients will eventually need further treatment. “This might give you a bit of pause, if you consider that these therapies currently cost about half a million dollars,” she commented.

CAR-T is being evaluated in less heavily pretreated patients (after 1–3 lines), such as KarMMa-3. In this study, median PFS was 13.3 months with standard therapy (hazard ratio, 0.49; P<.001). The sponsor of CARTITUDE-4 trial has also announced positive (unpublished) results. “We just don’t know the optimal sequence of these treatments yet. At our center, we tend to start with the bispecific T-cell engagers, because they are more readily available. For the fitter patients, we can start discussing and planning for CAR-T,” Dr. Callander said.

There are many other BCMA-directed CAR-T products in development, some offering the advantage of a much shorter manufacturing time. For example, production time is just 5 to 7 days with the NEXT-T product (CC-98633/BMS-986354). It is not yet clear which patients who experience disease progression on prior BCMA-directed therapies can benefit from BCMA-directed CAR-T therapy. There are, however, salvage therapies that may help patients who experience disease progression after CAR-T.

### Other Novel Agents on the Horizon

Among the novel agents in development are the oral cereblon E3 ligase modulators (CELMoDs) iberdomide.
and mezigdomide. Potentially “game-changing,” these immunomodulatory drugs may be more potent and have fewer side effects than lenalidomide and pomalidomide. In addition, modakafusp alfa is a first-in-class immunocytokine; given once monthly, it delivers attenuated interferon to immune and tumor cells in a highly targeted manner, which may improve efficacy and tolerability. Venetoclax (available, but not FDA-approved for myeloma) has shown activity in combination with daratumumab and carfilzomib and appears to be particularly effective in patients with t(11;14) disease.

References


