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Update on Novel Therapy of Relapsed Multiple Myeloma

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Abstract

In the last few years, carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, and daratumumab have all been approved by the Food and Drug Administration (FDA) for the treatment of relapsed multiple myeloma. Patients can now be treated at early or late relapse phases with the availability of agents or combination of agents that can be offered at each phase.

Abbreviations

FISH: fluorescence in situ hybridization

PIs: proteasome inhibitors

LEN: lenalidomide

IMiD: immunomodulatory drug

Introduction

Multiple myeloma is considered an incurable disease due to the emergent of resistant clones and often eventual relapse in the majority of patients [1]. A rise in serum or urine paraprotein in the absence of clinical signs or symptoms of myeloma is defined by IMWG criteria as biochemically relapsed myeloma. Clinical relapse is defined by worsening of myeloma markers. However, there is no set level of serum or urine paraproteins that consistently corresponds to the development of symptoms. Even in the same patient, paraprotein levels at different time points may produce variable symptoms [2]. Early and later relapses are not formally defined. A relapse occurring within 1 year of the last line of therapy is considered early [3], and is usually aggressive and dismal. Relapse which occurs >1year after the last line of therapy is considered later relapses [3]. Relapses (>24 months) generally have a more indolent course [1].

Patient evaluation at relapse

The key assessment at relapse is evaluation of M-protein in blood. Creatinine clearance and serum FLC are assessed routinely at relapse [3]. Imaging should be performed to assess for presence of active bone disease, new lytic lesions and extramedullary disease [4]. Skeletal X-ray survey is no longer standard practice. PET-CT for example, is favored, if there is a clinical suspicion of extramedullary progression or if serum lactate dehydrogenase is high [3]. Bone marrow evaluations at relapse may be of value in longstanding disease with "light chain escape" or even complete cease of M-protein production [3]. A bone-marrow biopsy should be considered in standard-risk patients to re-evaluate cytogenetic risk [4]. Cytogenetic assessment may become increasingly important for selection of relapse therapy [3].

Patient risk status at relapse

Risk assessment at relapse should include bone marrow examination with limited interphase fluorescence in situ hybridization (FISH) panel for new high-risk myeloma abnormalities (secondary abnormalities) including 17p deletion and 1q amplification. Their acquisition during progression is typically associated with more aggressive disease behavior and shorter survival. No need to repeat FISH for primary abnormalities (translocations and trisomies) if seen in the initial diagnostic marrow, since they do not routinely change during the course of the disease. Other risk factors such as renal insufficiency, age, presence of plasma cell leukemia/circulating plasma cells, extramedullary disease, and frailty, should also be considered [2].

The timing for initiation of treatment at relapse

Treatment options for biochemically relapsed myeloma: Treatment of biochemically relapsed myeloma depends on the patient's tolerance to prior treatment, rate of rise of myeloma markers, cytogenetic risk, presence of comorbidities (ie, neuropathy, and renal

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insufficiency), frailty, and patient preference. Patients with slowly progressive and asymptomatic relapse should be closely observed for symptoms and organ function with frequent assessment of myeloma paraprotein levels [2] every 1 to 2 months [1]. High-risk patients as defined by high risk cytogenetics, extramedullary disease, and/or evidence of rapid rise in myeloma markers and early relapse post-transplant/initial therapy should be treated immediately [2].

Treatment options for clinically relapsed myeloma: Whether to start treatment or not requires individualization based on re-evaluation of the patient's disease, consideration of the patient's prior tolerance to chemotherapy, and preference [4]. Immediate treatment should be initiated in relapsed myeloma patients with evidence of active disease as defined by presence of CRAB (hypercalcemia, renal dysfunction, anemia, lytic bone lesions) or other manifestations attributable to myeloma, such as extramedullary disease or central nervous system myeloma [2]. Bone marrow reserve is an important concern in patients with prior stem cell transplants, long term IMiD therapy or those previously received alkylating agents [1].

a) Treatment options for patients at first relapse: Relapse soon after discontinuing therapy or within 18 months of ASCT or while receiving maintenance therapy suggests high-risk disease regardless of their cytogenetic or FISH abnormalities. These patients should be considered to have more aggressive disease [2].

i. Indolent relapse or frail patients: can be treated with oral regimens such as IRd or Pd [4].

ii. Relapse with no prior transplant: Salvage or delayed ASCT should be offered as a consolidation therapy to transplant eligible relapsed multiple myeloma patients if ASCT is not received after primary induction therapy [2].

iii. Relapse with prior SCT: Treatment options for relapsed multiple myeloma after an ASCT include a second ASCT, novel chemotherapy regimens, or a non myeloablative allo SCT in selected cases, preferably as a part of a clinical trial [2].

- Repeat SCT may be considered in relapsed multiple myeloma if progression-free survival after first transplant is 18 months or greater [2].
- Chemotherapy: Relapsed patients during therapy or < 6 months of completing therapy are less sensitive to initial treatment regimen that successfully controlled multiple myeloma [2]. Patients will likely to respond to these agents when relapse occurs more than 6 months after stopping therapy [5].Triplet therapy should be administered on first relapse. A triplet is defined as a regimen with two novel agents (PIs such as ixazomib, bortezomib, or carfilzomib, immunomodulatory drugs as lenalidomide, pomalidomide, or thalidomide, or monoclonal antibodies such as daratumumab and elotuzumab) plus steroids [2].
- When selecting treatment at first relapse,the patient's tolerability to prior therapies, and comorbidities should be considered [2]. Patients who relapse while not on LEN maintenance should not be considered LEN refractory [1]. Current ESMO guidelines recommended Rd or an Rd-based triplet (e.g., DaraRd, KRd, IRd, or EloRd) for patients at first relapse after frontline bortezomib treatment and recommended bortezomib-based regimens such as DaraVd, Panobinostat-Vd, EloVd, or bortezomib plus cyclophosphamide and dexamethasone (VCD), or proteasome inhibitor-based doublets (Kd, Vd) for patients at first relapse after receiving an IMiD-based therapy [3]. A monoclonal antibody–based regimen in combination with an immunomodulatory drug and/or PI should be considered. In double-refractory cases, pomalidomide combinations with monoclonal antibodies or cyclophosphamide are reasonable options [2].
- There have been no head-to-head comparisons between the newer agents [3].
- Relapsed multiple myeloma who are responding to treatment have to continue treatment until disease progression or until unacceptable toxicity. There is clinical benefit for maintaining a longer duration of therapy at first relapse. There are not enough data to recommend risk-based versus response-based duration of treatment (such as MRD) [2].

b) Treatment options for patients at second relapse: survival benefits, along with the depth and duration of response are the important treatment goals in relapsed patients. Cytogenetics and fitness are important for treatment selection. Neither quality of life nor tolerability is considered as important as treatment response and duration at first relapse, i.e., some toxicities are accepted in order to achieve long-term benefits [6]. The Food and Drug Administration (FDA) have approved carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, and daratumumab for the treatment of relapsed multiple myeloma in the last few years, for further improvement in outcome [4]. Pomalidomide is increasingly the backbone of treatment at second relapse [3]. It has significant results in very advanced relapses including LEN-refractory cases and high-risk cytogenetic diseases [1]. Daratumumab monotherapy is being used in some countries [3].

The ESMO guidelines recommend, a pomalidomide plus dexamethasone (PomD)- backbone in combination with cyclophosphamide, ixazomib, bortezomib, daratumumab, or elotuzumab; or daratumumab as monotherapy or in combination; or enrolling the patient into a clinical trial of a novel therapy at second or subsequent relapse [3]. Alkylating agents can still have a role in relapsed myeloma when used in the appropriate setting [5].

Treatment duration is not a relevant question since therapy is usually continued until the next progression [6]. In some regimens such as those employing parenteral proteasome inhibitors it may be reasonable to stop therapy once a stable plateau has been reached to minimize risks of serious toxicity [4].

c) Patients with multiple relapses and disease that is refractory to all drug classes:Options for these patients include bendamustine containing regimens such as bendamustine, lenalidomide, dexamethasone or bendamustine, bortezomib, dexamethasone. Other options include the addition of panobinostat to a proteasome-inhibitor containing regimen, or the use of quadruplet regimen in which daratumumab is added to a standard triplet regimen. Venetoclax appears to have single-agent activity in multiple myeloma patients with t(11;14) subtype [4]. Allogeneic transplantation is an option as well for young high-risk patients with a suitable donor [4].

d) Regimens useful under certain circumstances for previously treated MM: bendamustine, high dose cyclophosphamide, DCEP, and DT-PACE, VTD-PACE are useful therapeutic options for previously treated MM patients under certain circumstances as recommended by NCCN guidelines [1].

Emerging Options

Novel agents

Several investigational approaches are promising. Agents with single-agent activity include isatuximab (a CD38 monoclonal antibody), marizomib (a new proteasome inhibitor), oprozomib (an oral proteasome inhibitor related to carfilzomib), filanesib (a kinesin spindle protein inhibitor), dinaciclib (a cyclin dependent kinase inhibitor), and LGH-447 (a pan PIM kinase inhibitor). Selinexor, a first in class oral selective inhibitor of nuclear export (SINE), which blocks the action of the protein XPO1 found within the nucleus of myeloma cells resulting in the accumulation of tumor suppressors, inhibition of NF-kB and suppression of several oncoproteins [4].

New immunotherapy strategy

Two of the most exciting options include antigen receptor T

cells (CAR-T) targeting B cell maturation antigen (BCMA) such as bb2121and GSK2857916 (a humanized anti-BCMA antibody that is conjugated to monomethyl auristatin-F (a microtubule disrupting agent) [4]. Bispecific T-cell engager (BiTE) is a single-chain variable fragment (scFv) composed of two linked mAbs (bispecific antibodies) that mainly target CD3 on the surface of T cells and tumor associated antigens. This unique structure allows BiTE to engage T cells with tumor cells promoting antitumor cytotoxicity and cytokine production [1].

Conclusion

Many factors influence clinician decision making regarding therapy of relapsing patients such as bone marrow reserve, survival benefits, along with the depth and duration of response. Some toxicities are accepted in these patients in order to achieve long-term benefits.

References

1. Bazarbachi AH, Al Hamed R, Malard F, Harousseau J-L, Mohty M. Relapsed refractory multiple myeloma: a comprehensive overview. Leukemia 2019 Oct;33:2343-2357.
2. Mikhael J, Ismaila N, Lacy M, Lipe B, Little RF, et al. Treatment of multiple myeloma: ASCO and CCO Joint Clinical Practice Guideline. JCO. 2019 Apr;37:1-39.
3. Mateos MV, Ludwig H, Bazarbachi A, Beksac M, Bladé J, et al. Insights on multiple myeloma treatment strategies. HemaSphere. 2019 Feb;3:1
4. Rajkumar SV.Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management. Am J Hematol. 2018 Aug;93:1091-1110.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Multiple myeloma. Version 1.2020.
6. Sklavenitis–Pistofidis R, Bustoros M, Ghobrial IM. Bone marrow niche in multiple myeloma and its precursor state. HemaSphere. 2019;3:S2.