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RESEARCH ARTICLE

The Age of Immune-therapy in Multiple Myeloma with a Collective Goal for a Cure

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ABSTRACT

Since the year 2000, we have seen unprecedented improvement in newly diagnosed multiple myeloma in terms of progression-free survival and a doubling of overall survival in 2009 from 2.5 years to 5 years. Patients treated now expect a median survival of 7.5 years, while those receiving quadruplet therapy, stem cell transplant, and consolidation and maintenance therapy have an expected survival up to 11 years.

Factors contributing to these improved outcomes include novel agents, antibodies, B-cell Maturation Agent-directed therapy, chimeric antigen receptor T-cells, bispecific antibodies, selective use of stem cell transplant, and supportive care measures such as bisphosphonates, prophylactic antimicrobials, cytokines, and intravenous immunoglobulins. Incorporation of these novel therapies in conjunction with increasing understanding of the genomic landscape of multiple myeloma and the evolving use of minimal residual disease negativity should persuade the oncology community to treat patients with high-risk smoldering multiple myeloma and guide treatment of early relapse in patients with newly diagnosed multiple myeloma. Here, we review early interventions within the context of genomic changes, minimal residual disease status, and strategies for treating high-risk smoldering multiple myeloma and standard and high-risk newly diagnosed multiple myeloma to improve progression-free survival, overall survival, and provide context for which patients may be considered cured.

Introduction

A significant number of interventions such as novel agents for treatment of multiple myeloma (MM), supportive care measures, and innovative treatments in newly diagnosed multiple myeloma (NDMM) have resulted in a tripling in survival rates over the last 23 years. Several changes over the last two decades, including redefining risk-factor categories, incorporation of minimal residual disease (MRD) status into treatment algorithms, quadruplet induction therapy, immediate or delayed stem cell transplantation, use of novel agents for consolidation and maintenance therapy have added a bewildering number of options for the treating oncologist. Here, we review the role of early detection of myeloma, interventions in the smoldering multiple myeloma (SMM) setting, standard-risk optimum therapy, incorporating B-Cell Maturation Antigen (BCMA) agents such as chimeric antigen receptor (CAR) T-cells, bi-specific antibodies, and emerging novel agents. Similarly, the use of genomic studies from marrow and blood can provide early determinations on treatment intervention. The advances in the detection of, treatment of, and monitoring of MM leads us to believe that creating a chronic disease or even the possibility for cure can now begin to be realized in NDMM patients. We present here a critical overview of interventions and treatments to pursue in our quest for a cure.

Novel Agents

Beginning in the year 2000, Thalidomide was the first novel agent applied to MM followed shortly by lenalidomide then bortezomid. These agents, in conjunction with more recent therapies, have led to a combination of doublet, triplet or even quadruplet therapies.[1] These combinations have also benefited patients who are not candidates for autologous stem cell transplant, increasing both progression free survival (PFS) and overall survival (OS).[2] Confounding factors such as a reduction of early mortality (within the first six months of diagnosis) declined from 10%-14% to 6.8% with utilization of novel agents,[3] lead-time bias with earlier diagnosis, and better supportive care measures also contribute to these improvements. Presently, in this era of novel agents, median survival for newly diagnosed multiple myeloma has increased from 2.5 to nearly 7 years.

Smoldering Multiple Myeloma

Newly diagnosed multiple myeloma always begins its journey with Monoclonal Gammopathy of Undetermined Significance (MGUS). Smoldering multiple myeloma (SMM) represents the transition stage between the two entities. Outcomes of SMM are quite variable with overt MM diagnosed at a rate of 10% per years 1-5, 3% years 6-10 and 1% per year thereafter.[4] Currently, high-risk multiple myeloma is defined as having two or three of the following: bone marrow plasma cell content greater than 20%; monoclonal protein greater than 2g. dl; involved/uninvolved free light chain ratio greater than 20. Regardless of risk status, standard of care (SOC) for SMM has been careful observation until meeting conventional diagnostic criteria. Given the higher risk of progression to symptomatic MM, as compared to MGUS, investigators have struggled with the concept of whether and when to treat SMM.

The first trial to investigate treating SMM was the QuiRedex study by the Spanish Myeloma Group.[5] In this study, patients with high-risk SMM were randomized to either 9 cycles of induction lenalidomide 25 mg days 1-21 with dexamethasone 20 mg days 1-4 and 12-15 in a 28-day cycle followed by maintenance lenalidomide 10 mg daily days 1-21 of a 28 day cycle for two years or observation only. The primary end point of the study was time to progression (symptomatic disease). 79% of patients in the treatment arm achieved a response to the induction phase and that proportion increased to 90% with the addition of maintenance lenalidomide. With the most recent update of the trial, the median time progression in the treatment arm has not yet been reached vs. median time to progression of 23 months in the observation arm. Importantly, the OS was higher in the treatment arm compared to observation. At five years, the OS was 88% in the treatment arm vs. 71% in the observation arm. This trial suggests that early intervention in SMM can delay or prevent transition to MM.

The randomized study E3A06 evaluated 182 patients with SMM to compare observation to treatment with lenalidomide 25 mg daily for three weeks in a four week cycle. The primary end point for the study was PFS, where progression was defined as biochemical progression and onset of end organ damage. The overall response rate (ORR) in the treatment arm was 50%. The PFS at 1, 3, and 5 years in patients receiving lenalidomide was 98%, 93%, and 91% compared to PFS of 89%, 76%, and 66% in the observation arm. The PFS was improved with lenalidomide vs observation with a HR of 0.28 and 95% CI 0.12-0.62. The improved PFS was greater for patients with high-risk disease as defined by the May 2018 risk model.[6]

In the era of novel treatments with well-tolerated adverse effects, the studies mentioned above as well as others not reviewed in this article, compel the oncology community to move away from observation as standard of care for SMM and offer treatment to those with high-risk SMM.

Genomics

The ability to identify high-risk patients with SMM or NDMM before major clonal expansion and end-organ damage should allow for earlier intervention and prevention. Furthermore, these early interventions should be guided by genomic events in MGUS and SMM. Indirect markers of disease burden can only identify a small percentage of patients actively progressing to symptomatic MM. Current risk models provide average probability of progression to MM; however, using novel, more robust biomarkers may further define a patient's absolute risk. With the use of next generation sequencing (NGS), whole exome and transcriptome sequencing, the genetic alterations of malignant plasma cells have promising potential to serve as more robust biomarkers. These technologies can be used to interrogate bone marrow microenvironment, potentially uncovering genetic signatures of clonal evolution, survival, and progression.[7] Furthermore, the same technologies can be applied to interrogating easily accessible circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA).[8] While common cytogenetic assays have shown MYC translocation,[9] chromosomal deletions and translocations such as t(4:14), t(14;16), t(6:14), and t(11:14) occur early in disease, more sensitive DNA sequencing has shown SNVs involving DNA repair and MAPK pathway are associated with disease progression.[10] Single, gene-based signatures in the RNA-editing enzyme APOBEC have emerged as the most prevalent and sensitive defining genomic event differentiating progressive from stable disease.[11] With this information, Bustoros has proposed the first genomic-based progression score for SMM which include MAPK, DNA repair, and MYC translocations.[10] This finding highlights the importance of integrating genomics to significantly improve our prediction models. Early identification of a malignant potential allows opportunities for early intervention. This approach will require validation.

Minimal Residual Disease

Minimal residual disease status has outpaced serum protein electrophoresis and immunofixation as a more sensitive tool for response assessment in MM. Minimal residual disease negativity is prognostic for both progression-free survival (PFS) and overall survival.[12] Minimal residual disease can be quantitated by multiparameter flow cytometry and NGS; however, NGS has the ability to detect one malignant cell among 10^6 normal nucleated cells (10^6), the most sensitive technique for determining MRD negativity. The use of PET/CT imaging negativity complements MRD negativity, as defined by the IMWG. A higher sensitivity threshold in the MASTER Trial[13] for high-risk patients demonstrated MRD of 10^{-6} had a 2-year PFS of 91% compared to 81% in those MRD of $^{10-5}$. Loss of MRD negativity status heralds relapse. The optimal time points for MRD testing and comparison with conventional surrogate markers are ongoing. Additionally, the use of mass spectrometry to quantitate circulating monoclonal proteins instead of electrophoresis and immunofixation, promises to increase clinical sensitivity with respect to progression.[14] At this time utilization of MRD remains under intense investigation to determine duration of maintenance therapy, duration of consolidation therapy, benefit of SCT to convert MRD positive to MRD negative disease, and offering earlier interventions in the upfront setting.

Monoclonal antibodies

Several advances in treatment have occurred within the last eight years, including the use of monoclonal antibodies. CD38 is cell surface glycoprotein that is expressed on several hematopoietic cells including myeloid cells, lymphoid cells and myeloma cells. Daratumumab is the first in-class fully human IgG monoclonal antibody targeting CD38 for use in treatment of multiple myeloma. It was first granted accelerated approval by the FDA in 2016 as monotherapy for patients with MM refractory to proteasome inhibitors and immunomodulatory agents, based on pooled analysis of the GEN501[15] and SIRIUS trials.[16] In short order following the seminal, single agent approval, the FDA approved the use of daratumumab, due to its high safety profile, in combination with lenalidomide and dexamethasone in patients with RRMM who received at least one prior therapy. This approval was based on results of the POLLUX trial.[17] In this phase 3 trial, 569 patients with MM who had received at least one prior therapy were randomly assigned to daratumumab with lenalidomide and dexamethasone or lenalidomide and dexamethasone alone. The 12 month PFS rate in patients treated with daratumumab, lenalidomide, and dexamethasone was 83.2% compared to 60.1% in patients treated with lenalidomide and dexamethasone alone? Furthermore, 22.4% of patients receiving daratumumab achieved MRD-negativity compared to 4.6% in the control group, where MRD negativity was defined as one tumor cell per 100,000 WBCs. Similarly, the FDA approved daratumumab in combination with

bortezomib and dexamethasone in patients with RRMM based on results of the 2016 CASTOR trial[18] and in combination with carfilzomib and dexamethasone, based on results from the CANDOR trial.[19]

The FDA has also approved the use of daratumumab in patients with newly diagnosed MM based on several clinical trials. The phase II GRIFFIN trial explored the addition of daratumumab to RVD in transplant eligible patients compared to induction with RVD alone.[20] The addition of daratumumab to thalidomide, bortezomib, and dexamethasone before and after autologous stem cell transplant improved the depth of response as demonstrated in the CASSIOPEIA trial.[21] For transplant ineligible patients, the addition of daratumumab to lenalidomide and dexamethasone improved PFS compared to lenalidomide and dexamethasone alone as demonstrated in the MAIA trial.[22]

In summary, daratumumab is the first in-class monoclonal antibody targeting CD38 and has been approved for use in patients with NDMM as well as patients with RRMM.

Isatuximab is an IgG1 monoclonal antibody that targets CD38 but at a different epitope compared to daratumumab. It was approved by the FDA in 2021 for patients with RRMM who received one to three prior lines of therapy based on the IKEMA study.[23] In this trial, 302 patients were randomly assigned in a 3:2 fashion to receive either isatuximab plus carfilzomib and dexamethasone or carfilzomib and dexamethasone alone. The median PFS in the isatuximab group had not yet been reached at data cut off, compared to a median PFS of 19.15 months in the carfilzomib and dexamethasone group.

The gene SLAMF7 was identified as a possible target for ADCC when Hsi and colleagues showed the humanized antibody HuLuc63 was responsible for antimyeloma activity in pre-clinical models.[24] In 2015, the FDA granted approval for use of the SLAMF7-directed monoclonal antibody elotuzumab for use in combination with lenalidomide and dexamethasone based on the results of the ELOQUENT2 trial. In this phase III trial, patients with RRMM who received one to three lines of previous therapy were randomized to receive elotuzumab with lenalidomide and dexamethasone or dexamethasone alone. At a median follow up of 24.6 months, the median PFS rate in the elotuzumab group was 19.4 months compared to 14.9 months in the control group. The trial also demonstrated the ORR was 79% in the elotuzumab group vs. 66% in the control group.[25]

Based on the ELOQUENT-3 trial, elotuzumab was approved by the FDA for use in patients with RRMM who previously received one three prior lines of therapy. In the trial, the combination of elotuzumab, pomalidomide, and dexamethasone improved the PFS to 10.3 months compared to 4.7 months in patients treated with pomalidomide and dexamethasone alone.[26]

Antibody-drug conjugates

BCMA is a cell surface protein whose surface expression is relatively restricted to normal and malignant plasma cells and has been correlated with plasma cell survival[27] and circulating levels of free BCMA have been correlated with prognosis. Given its association with expression on myeloma plasma cells, and role in plasma cell maintenance, BCMA has long been considered an ideal target for myeloma therapy.[28] Belantamab mafadotin (BM) is an IgG1 humanized monoclonal antibody conjugated to the cytotoxic drug monomethyl auristatin F.[29] Despite early modest, success in the DREAMM-2 trial,[30] where the ORR in patients treated with 2.5mg/kg was 31%, the manufacturer of BM, GlaxoSmithKline, withdrew regulatory approval in November 2022 as the DREAMM-3 trial failed to meet its primary endpoint of PFS.

Despite voluntary withdrawal of BM, several other ADCs are being explored as potential therapy in MM.

Chimeric Antigen Receptor T-cells

Chimeric antigen receptor (CAR) T-cell therapy utilizes engineered T-cells to target cell surface antigens on tumor cells, which leads to T-cell activation, T-cell expansion, cytokine production, release of cytotoxic substances such as perforins and granzymes which lead to tumor cell death. In 2017, the FDA approved the first two CAR-T cell therapies: tisagenlecleucel to treat relapsed B-cell acute lymphoblastic leukemia and axicabtagene ciloleucel to treat relapsed diffuse large B-cell lymphoma. Since 2017 the use of CAR T-cell therapy has expanded into other hematologic malignancies including multiple myeloma.

Successive generations of CARs have improved upon cytotoxic efficacy and persistence. Current FDA approved CAR T-cell products are second and third generation which contain intracellular costimulatory domains. Several investigators are exploring fourth generation CARs which express chemokines, cytokines, and a suicide gene to further enhance cell killing as well as safety.[31]

BCMA has proven to serve as a valuable target for CAR technology. Idecabtagene vicleucel (Ide-cel) was the first FDA approved CAR T-cell therapy in RRMM. Ide-cel is a CAR construct containing a mouse BCMA-targeting single-chain variable fragment as well as a 4-1bb costimulatory domain. The phase 1 CRB-401 clinical trial demonstrated an ORR of 85% in patients with heavily pretreated RRMM.[32] Furthermore, all 16 patients who had a partial response or better were found to MRD-negative at 10^{-4} nucleated cells or better, 15 of 16 were MRD-negative at $^{10-5}$ nucleated cells or better, and 3 of 16 were MRD-negative at 10^{-6} nucleated red cells.

In the follow up phase 2 KarMMa study, Ide-cel had an ORR of 73% in heavily pretreated RRMM patients.[33] 33% of patients had a complete response or better. MRD-negativity, defined as 10^{-6}, was achieved by 26% of all treated patients and in 79% of the patients who achieved a complete response.

Ciltacabtagene autoleucel (Cilta-cel) is the second FDA-approved CAR T-cell therapy. Like Ide-cel, Cilta-cel contains a 4-1bb costimulatory domain but it also harbors two BCMA-targeting domains. The phase 1/2b CAR-TITUDE study, 97 patients with RRMM were treated with Cilta-cel. [34] The ORR was a remarkable 97% with 67% of patients achieving a sCR at a median follow-up of 12.4 months. At the December 2022 ASCO presentation and at a median follow up of 27.7 months, 82.5% of patients achieved a sCR. Additionally, the median PFS and OS had not yet been reached.

Several other BCMA-directed CARs, several other myeloma targets are being explored and utilized for Cars. The targets include CD38,[35] SLAMF7,[36] GPRC5D,[37-38] CD139, and transmembrane activator and CAML interactor (TACI).

In addition to new myeloma targets for CAR T-cell therapy, allogeneic, or so called "off the shelf," CAR T-cell therapy is being investigated. Given the time requirement to develop patient-specific autologous CAR T-cells, during which some patients require bridging therapy, allogeneic sources or CAR T-cells are under investigation for shorter and quicker CAR-T production. Mailankody and colleagues report on the first-in-class allogeneic BCMA-targeting CAR-T: allo-715.[39] 48 patients with RRMM were given escalating doses of allo-715. The ORR was 55.8%. 24 patients received allo-715 along with a lymphodepletion regimen consisting of fludarabine, cyclophosphamide, and anti-CD52 antibody. Of these patients, eleven achieved a VGPR or better, and six achieved a complete response. Other clinical trials are investigating allogeneic CAR-T directed against CD19 and SLAMF7.

Bispecific antibodies

Bispecific antibodies (BsAbs) were designed to build upon the success of monoclonal antibodies such as daratumumab and elotuzumab. Unlike monoclonal antibodies, BsAbs recognize two antigens: one the target tumor cell and one on an immune effector cell. Dual recognition results in bringing cytotoxic T cells into close proximity to malignant plasma cells for a more targeted cytotoxic effect.[40] BsAbs can be classified as either IgG-like or non-IgG-like. Bispecific T-cell Engagers (BiTEs) are a non-IgG-like subclass of BsAbs. Technically, BiTEs are a recombinant protein made up of two single chain variable fragments linked together.[41]

Teclistamab was the first bispecific antibody approved for use in penta-refractory MM, or disease that is refractory to two immunomodulating agents, two proteosome inhibitors and a CD38-based therapy. In October of 2022, the FDA approved teclistamab based on results from phase I/II MajesTEC-1 study. Teclistamab is a humanized Fc IgG anti-BCMA and anti-CD3 bispecific antibody. In the MajesTEC-1 study, 165 patients with triple-exposed relapsed/refractory multiple myeloma received teclistamab.[42] the median number of previously received therapies was five. After a median follow-up of 14.1 months, the overall response rate was 63% with 39.4% of patients achieving a complete response or better. In the overall study population, the MRD-negative rate was 26.7%, but in patients who achieved a complete response or better, the MRD-negativity rate was 46%. The median duration of response was 18.4 months and the median PFS was 11.3 months. Adverse events in the MajestTEC-1 study included cytokine release syndrome, neutropenia, anemia, and thrombocytopenia. Five patients (3%) experienced grade 1 or grade 2 immune effector cell-associated neurotoxicity syndrome.

Talquetamab was the first BsAb to target GPRC5D and CD3. It gained accelerated FDA approval for RRMM patients who received at least four lines of therapy in August 2023. Approval was based on results of the MonumenTAL-1 study.[43] in this study, 100 patients received talquetamab 0.4mg/kg weekly after two step-up doses the first week and 87 patients received 0.8mg/kg every two weeks after three step up doses the first week. The ORR in the weekly dosing arm of talquetamab was 73% with a median DOR of 9.5 months. For the 87 patients receiving every other week dosing of talquetamab, the ORR was 73.6% and the median

DOR was not estimable. Overall, 85% of patients maintained a response of nine months.

At the time of writing this article, the FDA approved elranatamab for relapsed/refractory multiple myeloma. Approval was granted based on the results of the MajesticMM-3 trial.[44] This phase II trial enrolled 97 patients who were BCMA-naive (cohort A) and 64 patients who were previously exposed to BCMA-directed therapy (cohort B) received escalating doses of elranatamab. In BCMA-naïve patients, the overall response was 57.7% with 25.8% of patients achieving a complete response. With a median follow-up of 11.1 months, the 6-month and 9-month duration of response rates were 92.4% and 82.3%, respectively. In patients who received prior-BCMA therapy, the overall response rate was 33.3%. With additional follow up and at the time of reporting findings from this study at the 2023 EHA congress, the duration of response, PFS, and overall survival were not yet met in BCMA-naive patients.

Similar to CARs, several new targets are being explored for bispecific antibodies including FCRH5,[45-46] CD38,[47] and CD138.[48-49]

New Frontiers in novel antibodies: Natural killer cells and trispecific antibodies

Several groups are looking at using BsAbs that target myeloma cells and natural killer (NK) cells instead of T-cells. CD16 is a surface protein on NK-cells and serves as a target for the single chain variable fragment to attract NK-cells to the myeloma cells. The first BsAb to target NK-cells is AFM26 which also targets BCMA on myeloma cells.[50] Another variation of these novel antibodies include trispecific antibodies (TsAbs) with one single chain variable fragment targeting CD16 on NK-cells and two SCVFs targeting tumor targets, or two SCVFs targeting two T-cell antigens and one tumor target.

Treatment of Standard and High-Risk NDMM and the Role of SCT

The goal of therapy is to achieve the deepest negative MRD status by NGS, which equates with the longest survival. This applies to NDMM and RRMM patients, and is monitored for at least 12 months for false negative results. For standard risk, transplant eligible patients, the IFM/DFCI 2009 trial determined there was no difference in OS for patients treated with immediate vs. delayed SCT after induction therapy, although upfront SCT was associated with longer PFS utilizing induction lenalidomide, bortezomib and dexamethasone (RVD).[51] MRD negativity rate with induction therapy followed by immediate transplant was 20%.[52] In the Griffin Trial,[20] the addition of daratumumab to RVD in a randomized trial improved MRD rates from 32% to 62%. Consolidation therapy of 2-3 cycles after SCT has the potential to deepen CR rates. To date, consolidation has not added significant improvement in outcomes but could be considered in those who are MRD positive after SCT. High-risk patients (13.4% of NDMM patients) may benefit from a different line of therapy given during induction to try to eradicate MRD. Maintenance therapy is employed for at least two years or until progression, which adds a minimum of 2.5 years to OS.[53] There is no data regarding MRD with respect to duration of maintenance therapy, when we can consider stopping maintenance therapy, or alternatives to lenalidomide. Patients with standard-risk NDMM should be offered the best possible therapy to achieve MRD negative status. In non-transplant eligible patients, a monoclonal antibody with lenalidomide and dexamethasone or RVD should be the standard of care.[54]

High-risk patients currently include those with adverse cytogenetics, early relapse, or those with plasmacytoma and account for 13.4% of NDMM. Most MRD positive patients relapse within two years compared to those who are MRD negative. New strategies are required to eradicate MRD. One strategy to obtain and sustain MRD negativity in high-risk MM is to change treatment in the setting of suboptimal response.[12] Addition of newer therapies utilizing CAR T-cells or BsAbs targeting known and novel myeloma targets. New immunomodulatory agents such as iberdomide[55] and mezigdomide[56] have been shown to bind to the transcription factors Ikaros and Aiolos resulting in accelerated apoptosis compared to lenalidomide. These agents should be effective as the next line of imids in treating MM.

It has been felt by some that MM patients in a sustained CR for 10 years remaining MRD- and off therapy for at least a year should have a 40%-50% chance for cure.[57] Physicians will need to embrace early intervention with high-risk SMM, aggressive therapy for standard-risk NDMM, risk-adaptive treatment for high-risk patients utilizing anti-BCMA immunotherapies and bispecific T-cell engagers. The promise of better genomics and MRD status should help improve outcomes and the goal for cure.

Conclusion

We have reviewed the rapid accomplishments in the field of multiple myeloma. Physicians and researchers are increasingly attracted to this dynamic field. Myeloma is paving the way in

hematology/oncology much as what Hodgkin's and other lymphomas did with combination chemotherapy and what targeted and immunotherapy has done for solid tumors. The results over the last two decades in multiple myeloma suggest that early intervention with our best agents can result in a patient who may expect a better quality of life. Perhaps those off therapy and MRD negativity can achieve a cure. Genomics will identify those progression signatures underlying clonal evolution before actual disease progression takes place allowing for earlier interventions. Bi-specifics will become tri-specifics, CAR-T will be moved earlier into therapy. New novel agents will emerge. Risk-adaptive treatment pathways and algorithms will guide clinicians to make changes in multiple myeloma. Clearly, we have entered a new era in the treatment of multiple myeloma. The energy of innovation and adaptability will lead us forward towards significantly improved patient outcomes and meaningful cures. Indeed, these are exciting times!

Conflicts of interest: None

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