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Next Generation Antimyeloma Agents: A Review

Batinić J[1,2*], Aurer I[1,2], Dreta B[1], Bašić-Kinda S[1] and Nemet D[1,2]

[1]University Hospital Center Zagreb, Croatia

[2]School of Medicine, University of Zagreb, Croatia

***Corresponding author:** Josip Batinic, School of Medicine, University of Zagreb, Croatia

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Abstract

Multiple myeloma is still an incurable disaese despite major advances in treatment seen in the past decade. An increased knowledge about the myeloma pathogenesis led to a discovery of new potent drugs. Our goal is to discuss some of these new treatment options, mainly those that are already approved for the treatment of myeloma patients. Data on new generation of proteasome inhibitors (carfilzomib, ixazomib), new immunomodulatory agents (pomalidomide), monoclonal antibodies (daratumumab, elotuzumab), histone deacetylase inhibitors (vorinostat, panobinostat) and new immunotherapy options (CAR T cells) are presented in this manuscript.

Keywords: Multiple myeloma; Novel agents; Proteasome inhibitors; Immunomodulatory drugs; Monoclonal antibodies

Introduction

Multiple myeloma (MM) is a malignant hematological disease, the most frequent condition among plasma cell dyscrasias. It is characterised by proliferation of malignant monoclonal plasma cells, mainly in the bone marrow, but in a minor number of patient also/or as extramedullary tumor masses. Since monoclonal plasma cells maintane the ability of immunoglobulin production and secretion, MM is characterised by the presence of monoclonal protein in serum and/or urine; intact immunoglobuline molecule or immunoglobulin free light chains only. In rare cases the disease is non-secretory, that is monoclonal protein can not be detected in serum/urine but there is evidence of bone marrow monoclonal plasma cell infiltration, as well as signs and symptoms of the disease. Myeloma is a rare disease, but it is the second most frequent hematological disease, after non Hodgkins lymphoma, with the incidence of 6 per 100000 per year in the USA and Europe [1]. The median age at diagnosis is 69 years of age.

Symptomatic myeloma is preceeded by the premalignant condition called monoclonal gammopathy of undetermined significance (MGUS) which has the risk of progression to symptomatic disease of approximately 1% per year and asymptomatic or smoldering myeloma with greater risk of progression (approximately 10% in the first 5 years). This phenomenon is explained by the "two hit" theory which proposes two steps ("hits") in the developing of the disease. The first step is antigen stimulation and an abnormal response to it, which leads to limited clonal growth of the plasma cells, that is development of MGUS. In this phase mutations, particualry translocations involving chromosome 14 occur [2,3]. The second step is development of mutations of oncogens (such as MYC, KRAS, NRAS) which lead to dysregulation of cell cycle, apoptosis pathways which leads to progression to symptomatic myeloma [4]. It is believed that bone marrow microenviroment has also very important role in myeloma progression. In addition, recently it has been shown by genomic studies that myeloma is not generated by single tumor stem cell, but is derived from several genetically different subclonal population of tumor cells [1].

For establishing the diagnosis of symptomatic myeloma the patient has to meet diagnostic criteria (bone marrow plasma cells >10% and any or more of the myeloma defining events: evidence of end organ damage: hypercalcemia, renal insufficiency, anemia, lytic bone lesions; clonal bone marrow plasma cells >60%; serum free light chain ratio >100; >1 focal lesion of at least 5 mm in size on magnetic resonance imaging studies) [5]. The standard laboratory tools for screening, diagnosing and monitoring of the disease are: total serum protein, serum (urine) protein electrophoresis (SPEP/UPEP), qunatification of immunoglobulins, serum free light chains (sFLC) quantification, serum protein immunofixation, complete blood count, serum creatinine and electrolytes, namely calcium, lactat dehydrogenase (LDH) and β2 microglobulin. Besides these laboratory test, mandatory workup includes also skeletal survey (conventional X-ray, MRI or PET-CT) and bone marrow analysis (including cytogenetic and fluoresence in situ hybridisation (FISH) for the detection of del13, del17p13; t(4;14), t(11;14), t(14;16), 1q+) and/or soft tissue biopsy for solitary or extramedullar plasmocytomas. Results obtained from the laboratory workup are not used only for diagnosis and monitoring but also for staging and risk stratification; especially FISH analysis for the later. There are two classification: Durie Salmon which is in fact diagnostic and International Staging System (ISS) which is prognostic. Recently a new revised ISS was developed which incorporates findigns of chromosomal abnormalities detected by FISH and LDH levels [6].

The disease has very heterogeneous clinical presentation. In some patients the disease is non agressive, developing slowely and responds well to treatment while in other it has rapid, agressive course with treatment resistance and fast fatal outcome as result of that [7].

However, in the last decade a considerable improvement in survival of myeloma patients was observed and today the median overall survival is estimated to 6 years (in the period before year 2000, median overall survival was 3 years) [1,8]. This improvement is a result of the use of proteasome inhibitors (bortezomib) and immunomodulatory drugs (thalidomide and lenalidomide) both, in the newly diagnosed and relpased disease. The approach to MM treatment has not changed and patients are still classified in two groups: transplant elegible (age<65 years, no significant comorbidities) and transplant inelegible

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(age>65 years, sever comorbidites, frail). There is a general consensus that in both groups induction treatment should be based either on proteasome inhibitors (bortezomib based) or on immunomodulatory drugs and that triple combination (usually with corticosteroids and another antimyeloma agent like cyclophosphamide or adriamycin) is prefered to double combination. In patients who are candidates for high dose chemotherapy and autologous transplantation, three to four cycles of induction therapy are recommended before proceeding to stem cell harvesting and transplantation. Also in these patients melphalan should be avoided since it can compromise stem cell harvesting. The role of maintenance or consolidation therapy after transplantation is still a matter of debate. In patients who are not eligible for high dose chemotherapy several cycles of the same protocol (usually in the duration of 12 to 18 month) sholud be administered [9]. In relaps setting, the same regiment can be used if relaps occured more than 1 year after the initial treatment. If relaps occurs sooner, different regiment should be given according to patients condition and availability of the drugs.

Despite major improvements in patients outcomes observed during the last decade, multiple myeloma is still by definiton an incurable disease. For that reason there is a considerable space and need for further advances in treatment. The aim of this paper is to give an overview on several next generation antimyeloma agents.

Next generation antimyeloma drugs

Proteasome inhibitors

Carfilzomib: As menitioned before, first in class proteasome inhibitor bortezomib, inhibitor of the 26S proteasome, revolutionized MM therapy and has become a backbone of the treamtent of myeloma patients. Carfilzomib is the most prominent of the second generation proteasome inhibitors. It binds irreversibly to the 20S subunit of the proteasome and inhibits chymotrypsin-like domain. As a result, polyubiquitinated pro-apoptotic proteins (such as IκB family inhibitors) destined to be destroyed are accumulated in the malignant cell leading to inhibitions of cell cycle and promotion of programmed cell death. Preclinical data indicated that carfilzomib inhibits chymotrypsin-like domain more specifically than bortezomib, which is assocciated with different toxicity profile, mainly pertaining to peripheral neuropathy. Further more, it has been shown that there is a weak or even none cross resistance between bortezomib and carfilzomib [8]. In a phase II trial PX-171-003-A1 [10,11], carfilzomib demonstrated efficacy as a single agent therapy in relapsed/refractory settings with 80% of patients inrolled refractory and/or intolerant to both bortezomib and lenalidomide. Overall response rate (ORR) was 24% and clinical benefit response (ORR + minimal response) was observed in 36% of patients. Median duration of response was 7.8 months while median overall survival was 15.6 months. Based on these data, carfilzomib was approved by the U.S Food and Drug Administration (FDA) for the treatment of relapsed/refractory disease. A phase III trial that evaluated carfilzomib as a single agent was PX-171-011 (FOCUS) trial [12]. It compared carfilzomib (20mg/m^2 on days 1 and 2 of cycle 1; 27 mg/m^2 thereafter) and low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory myeloma (including patients previously exposed to bortezomib or IMIDs). The results were suprising: based on the phase II trial PX-171-003-A1, overall survival benefit was expected for patient in the carfilzomib group. However, the study showed similar overall survival and progression free survival in both groups (OS was 10.2 months in the carfilzomib group and 10.0 months in the control group; PFS was 3.7 and 3.3 months, respectively). Two clinical phase III trials demonstrated carfilzomibs great potential in combination with other agents. In the ASPIRE trial [13], combination of carfilzomib + lenalidomide + dexamethasone (KRd) was compared to lenalidomide + dexamethasone (Rd) in relapsed/refractory patients (carfilzomib dosing was the same as in the FOCUS study and it was administered for 18 cycles). Progression free survival was significantly improved with addition of carfilzomib compared to control group; median 26.3 months *vs.* 17.6 months (HR 0.69; CI 0.57 to 0.83; p=0.0001). 2-year overall survival rates were 73.3% in the carfilzomib group and 65% in the control group (HR 0.79; 95% CI 0.63 to 0.99, p=0.04). Overall response rates (partial response or better) were 87.1% in carfilzomib group and 66.7% in the control group (p<0.001) while complete respnse (CR) rates were 31.8% and 9.3% respectively. Also, benefit of the progression free survival was observed in the subgroups of patients previously exposed to bortezomib or lenalidomide as well as in the cytogenetic high risk group. Adverse event rates were similar (83.7% and 80.7% of patients in the carfilzomib group and control group respectively). Adverse events of specific interest included dyspnea (2.8% in the carfilzomib group *vs.* 1.8% in the control group), cardiac failure (grouped term, 3.8% *vs.* 1.8%), ischemic heart disease (grouped term, 3.3% *vs.* 2.1%) and renal failure (grouped term 3.3% *vs.* 3.1%). The second trial, ENDEAVOR [14], was the first trial that directly compared two proteasome inhibitors. In this trial patients with relapsed myeloma were randomized to carfilzomib + dexamethasone (Kd) group (carfilzomib starting dose was 20 mg/m2 on days 1 and 2 of cycle 1 and 56mg/m2 thereafter; carfilzomib was administered until progression) or bortezomib + dexamethasone group (Vd). Progression free survival was significantly better in the Kd group than in the Vd group (18.7 *vs.* 9.4 months, HR 0.53; 95% CI 0.44 to 0.65, p< 0.0001) while overall survival data were immature at the interim analysis. Progression free survival benefit was seen also in the subgroups of patients previously exposed to proteasome inhibitors and/or immunomodulatory agents, as well as in the cytogenetic high risk group. Overal response rates were 76.9% in the Kd group and 62.6% in the Vd group (p<0.0001). Especially interesting were very good partial response (VGPR) or better rates and complete response (CR) rates. In the carfilzomib group VGPR or better was acheived in 54.3% of patients *vs.* 28.6% in the bortezomib group, while CR rates were 12.5% in the carfilzomib group and 6.2% in the bortezomib group. In addition, the trial demonstrated significantly lower incidence of peripheral neuropathy in the carfilzomib group, but as seen in the previous trials dyspnea, hypertension, cardiac failure and renal failure were more frequent in the carfilzomib group (however, treatment discontinuation and treatment related death rates were comparable). A part from relaps/refractory settings, carfilzomib was also evaluted in the newly diagnosed myeloma patients in several phase II clinical trials. Two of these trials, one of carfilzomib in combination with cyclophosphamide and dexamethasone (Ccyd) and the other with the additon of thalidomide to the same combination (CYKLONE trial) showed promissing results in newly diagnosed myeloma patient [15]. Carfilzomib in combination with melphalan and prednisone in newly diagnosed transplant in-elegible patients is also potent and effective therapy with acceptable toxicity profile [17].

Ixazomib: Ixazomib is the first proteasome inhibitor that can be taken oraly. It also inhibits 20S subunit, reversebly binding to the chymotripsin-like domain. Several preclinical studies and phase I trials demonstrated synergistic effect with lenalidomide and dexamethasone and proved ixazomib to be effective antimyeloma agent with acceptable safety profile [7]. Based on these results, a phase III clincal trial was conducted evaluating combination of ixazomib and lenalidomide + dexamehtason (Rd) in comparison to Rd + placebo in 722 patients with relapsed/refractory myeloma [17]. Dose of ixazomib was 4 mg given on days 1, 8 and 15; lenalidomide dose was 25 mg (10 mg in case of renal damage) on days 1 through 21 and dexamethasone 40 mg on days 1, 8, 15 and 22. Primary end-point was progression free survival (PFS) which was significantly longer in the ixazomib, 20.6 months *vs.* 14.7 months in the control group (HR 0.74; p=0.01). Interestingly, PFS in patients with the high-risk cytogenetics was similar to that of the whole group. Also, PFS benefit was observed in the ixazomib group regardless of prior proteasome inhibitor or immunomodulatory agents exposure. Overall response rates were 78.3% in the ixazomib group and 71.5% in the placebo group while very good partial response or better rates were 48% and 39% respectively. Duration of response was 20.5 months in the ixazomib group and 15 months in the placebo group. The serious adverse events rate was similar in both groups (47% in ixazomib and 49% in placebo group), although thrombocytopenia grade 3-4, low grade gastrointestinal side-effects and rash were observed more frequently the ixazomib group. Based on the data from this trial, FDA approved ixazomib in the combination with Rd for treatment of myeloma patients who received at least one prior therapy.

Next generation immunomodulatory agnets

Pomalidomide: Pomalidomide is a new immunomodulatory drug that has several mechanisms of action. Besides the direct effect on myeloma cells, it also changes bone marrow microenviroment leading to inhibition of myeloma growth and vascular growth promotors. Some data indicate that pomalidomide stimulates cell mediated immune response against myeloma cells. Several phase II trials were conducted in relapsed/refractory setting in which pomalidomide showed great potential. In the first trial pomalidomide was given in combination with low-dose dexamethasone which led to response rate of 63%, including 40% of patients refractory to lenalidomide, 37% of patients refractory to thalidomide and 60% of bortezomib refractory patients. Median progression free survival in this group of patients was 11.6 months [18]. A phase III clincal trial (MM-003) in relapsed/refractory patients was conducted comparing pomalidomide + low-dose dexamethasone *vs.* high-dose dexamethasone and showed overall response rate of 35% in the pomalidomide group with median overall survival of 14.9 months [19]. In this trial 75% of patients were refractory to both bortezomib and lenalidomide. A secondary analysis on the same cohort of patients (MM-003 trial) showed that PFS and OS benefit are mantained regardless of type and number of prior therpies, with or without previous exposure to thalidomide, lenalidomide or bortezomib or refractory to bortezomib, lenalidomide or both [20]. As far as safety profile is concerned, pomalidomide exhibited acceptable toxicity, mainly hematological and increased risk of venous thromboembolism, like all other immunomodulatroy drugs [21]. Based on these data, FDA gave approval for the use of pomalidomide (alone or in combination with low-dose dexamethasone) for relapsed/refractory disease. Currently several clinical trials are being conducted investigating efficacy of pomalidomide in combination with other antimyeloma drugs (i.e., cyclophosphamide, pegylated liposomal doxorubicine, even carfilzomib) [22,23].

Monoclonal antibodies

Daratumumab: Daratumumab is a human IgG1κ monoclonal antibody which targets cell surface protein CD38, dominantly expressed on myeloma cells. CD38 is a transmembrane glycoprotein which has several roles by which promotes and sustains myeloma growth: regulates cell adhesion, interacts in the signal transduction within the cells but also between myeloma cells and T lymphocytes leading to immune tolerance [7,24]. Daratumumab has several mechanisams of antimyeloma effect. Some are well known, such as complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, antibody dependent cellular phagocytosis. Further more, there are data suggesting that daratumumab mediated depletion of newly discovered CD38 positive immune regulatory cells (immunosupressive regulatory cells that promote tumor growth) which leads to expansion of positive immune effector cells in the myeloma micorenviroment and better immune antitumor response [25]. Efficacy of daratumumab as single agent was first tested in the GEN501 trial [24] (phase I/II). Trial consisted of two parts: part 1 with 32 patients enrolled was dose escalation study and part 2 with 72 patients enrolled was dose expansion study. In part 2, patients had a median of 4 prior therapies and 79% of them were refractory to the last therapy. There were two cohorts: 30 patients received daratumumab at 8 mg/kg and 42 at 16 mg/kg. The overall response rate was 36% in the 16 mg/kg group (with 4 patients acheiving very good partial response or better) and 10% in the 8 mg/kg group (with 3 partial responses). Median duration of response was not reached in the 16 mg/kg group and was 6.9 months in the 8 mg/kg group. The median progression free survival was 5.6 months in the 16 mg/kg group *vs.* 2.4 months in the 8 mg/kg group, while median overall survival at 12 months was 77% in both groups. Another phase II trial investigating daratumumab as single agent in relapsed/refractory setting was SIRIUS trial [26]. In this trial overall response rate was 29.2% (with 3 patients acheiving even stringent complete response, 10 very good partial response and 18 partial response) and median duration of response was 7.4 months. Progression free survival was 3.7 months, while median overall survival was 17.5 months. Usmani, et al. performed a pooled analysis of patients included in the above mentioned trials. According to this analysis overall response rate with daratumumab monotherapy in relapsed/refractory disease was 31.1%, median duration of response was 7.6 months, median PFS 4.0 months and median overall survival 20.1 months. Based on these data daratumumab was approved for treatment of relasped/refractory myeloma patients by both the FDA and EMA.

Recently, impressive interim analysis of two still on-going phase III clincal trials were presented. In the CASTOR trial [27] patients with relapsed/refractory disease were randomised to bortezomib + dexamethasone (Vd) group or Vd + daratumumab group. Interim analysis showed that daratumumab significantly improved progression free survival (median PFS was not reached in daratumumab group *vs.* 7.2 months in the Vd group), time to progression and overall response rate (83% *vs.* 63%, p<0.0001) with the doubling of the very

good partial response or better rate (59% *vs.* 29%) and complete response rate (19% *vs.* 9%). On the last EHA meeting (21st European Hematology Association meeting held in Kobenhaven, Denmark, June 9-12, 2016) data from the POLLUX trial [28] were presented. In this trial in the same patient settings, lenalidomide + dexamethasone (Rd) was compared to Rd + daratumumab. As in the previous study combination of Rd and daratumumab proved to be superior to Rd alone in terms of progression free survival (PFS was not reached *vs.* 18.4 months), time to progression and overal response rate (93% *vs.* 76%).

Currently phase III trials in newly diagnosed myeloma patients are in progress: the ALCYONE study comparing brotezomib + melphalane + dexamethasone (VMP) alone or in combination with daratumumab in patients in-elegible for high dose chemotherapy and autologous stem cell transplantation and the CASSIOPEIA study comparing bortezomib + thalidomide + dexamethasone (VTD) and VTD + daratumumab in patients eligible for high dose chemotherpy and autologous stem cell tranplantation [26].

Elotuzumab: Elotuzumab is a humanized monoclonal antibody, class IgG1, against CS1 molecule (CS1 is also called SLAM F7; signaling lymphocyte activation molecule F7). SLAM F7 molecule is predominantly expressed on myeloma cells and natural killer (NK) cells and almost completely absent in other tissues which makes it a reasonable antimyeloma target although it exact role in myeloma tumorogenesis is still unclear [27]. Elotuzumab has dual effect by directly activating natural killer cells and mediating antibody dependent cell-mediated cytotoxicity [29]. In phase I trials elotuzumab as a single agent did not show very promising results, but preclinical studies indicated that it has a synergistic effect in combination with both proteasome inhibitors and immunomodulatory drugs. In one phase II study combination of elotuzumab and bortezomib + dexamethasone was compared to bortezomib + dexamethasone alone in relapsed/refractory setting [30]. Elotuzumab group had median progression free survival of 9.7 months *vs.* 6.9 months in the control group. There were no additional toxicities in the experimental arm. Based on these results, phase III trial was conducted; ELOQUENT 2 trial [31]. This trial was conducted also in patients with relapsed/refractory disease. They were randomized in two groups: one receiving lenalidomide + dexamethasone (Rd) with addition of elotuzumab and the second receiving only Rd. Analysis revealed significantly longer progression free survival in the elotuzumab group of 19.4 months compared to 14.8 months in the control group. Overall response rate was also better in the elotuzumab group compared to control; 79% *vs.* 66% respectively. The data from the ELOQUENT 2 study provided FDA approval for relapsed/refractory myeloma patients in combination with lenalidomide and dexamethasone. The ELOQUENT 1 trial is in progress comparing the same treatment regiments as in previous study but in newly diagnosed patients [7].

Histone deacetylase inhibitors (HDAC inhibitors)

Vorinostat: It was shown acetylation and deacetylation of histone proteins have impact on the mechanisms of chromatin transcription and consequently on gene expression. Especially interesting among histone protein is histone deacetylase 6 which, besides its role in acetylation of the chromatine structure, has additional function in the aggresome formation and degradation. Thanks to this function, inhibtion of HDAC 6 has sinergistic effect with proteasome inhibitors; both interrupting degradation pathways of accumulated proteins in the cells [32]. Data on vorinostat efficacy in multiple myeloma patients were obtained from two large phase IIb and phase III trials: VANTAGE 095 [33] and VANTAGE 088 [34]. The first trial included patients who were bortezomib refractory and intolerant to immunomodulatory agents. The primary end point was overall response rate which reached 17% but clinical benefit rate was higher 31%. Median duration of response was 6.3 months. The second trial compared bortezomib + vorinostat and bortezomib + placebo in relapsed but non refractory disease. Progression free survival was the primary endpoint: in vorinostat group it reached 7.63 months while in the placebo group 6.83 months. Although the PFS difference in the later study was statistically significant (p=0.01), results of the trial were not convincing enough to place vorinostat in the every day clinical practice. It seems that vorinostat may be a therapy option in patients refractory to bortezomib [35].

Panobinostat: Similar to vorinostat, data on panobinostat efficacy were obtained in trials comparing combinations with bortezomib +/- dexamethasone in relapsed/refractory settings. The PANORAMA 1 trial [36] was a phase III trial comparing bortezomib and dexamethasone in combination with panobinostat or placebo. Progression free survival was 12 months in the panobinostat arm and 8.1 months in the placebo arm (p<0.0001). The PANORAMA 2 trial [37] evaluated panobinostat in combination with bortezomib and dexamethasone in bortezomib refractory patients. Overall response rate was 34.5%, clinical benefit rate 52.7% and median PFS was 5.4 months. Both of these trials demonstrated superior efficacy in the panobinostat group in pretreated myeloma patients who received bortezomib and IMIDs based therapies. Especially noteworthy are results showing efficacy even in the bortezomib refractory patients, giving support for use of panobinostat in combination with bortezomib and dexamethasone in advanced relapsed and refractory multiple myeloma [36,37]. Based on these trials FDA approved panobinostat in combination with bortezomib and dexamethasone for treatment of relapsed/refractory myeloma patients who had at least two prior lines of therapy.

Immunotherapy

Chimeric antigen receptor T cell therapy: Adoptive T cell immunotherapy has become one of the hot topics in recent years. Especially chimeric antigen receptor T cell therapy or CAR T cell technology which has been tested in a number of B cell malignances and showed impressive and promissing results. The method is based on modification of T cell receptor through genetic engineering. In this process extracellular antigen binding domain of the T cell receptor is replaced with single chain variable fragment derived from a monoclonal antibody with high specifity for selected target on cell surface [38]. This enables such modified T cells to acitvate independently of major histocompatibility complex (MHC) molecules, thus making them insensitive to tumor escape by downregulation of MHC molecules. In case of mutiple myeloma there are several clinical trials in progress with different targets for CAR T cells: kappa light chain, cell surface difucosylated carbohydrates coupled to cell surface proteins, CD138 [29]. There are still numerous open issues regarding this technology such as saftey profile, target selection, patient population to be treated. Recently, a case report describing activity of anti CD19 CAR

T cells in myeloma patient [39] was published as well as report on 6 patients treated with CAR T cells directed against B cell maturation antigen (BCMA) [40] showing promissing results. But as mentioned above, more data from clinical trials will have to be obtained before this method becomes available outside clinical trials [41,42].

Conclusion

In the last 15 years we have witnessed major advances in myeloma treatment and significant improvement in myeloma patient outcomes. This was mainly due to introduction of bortezomib and lenalidomide as backbone drugs in treatement of both transplant eligible and transplant in-elegible patients. But, as mentioned before, multiple myeloma is stil an incurable disease, with its natural course consisting of periods of remission and relapses leading in the end to refractoriness and fatal outcome. Hence the need for next generation agents which will be able to overcome refractoriness to nowdays standard therapies.

In this paper we focused on next generation antimyeloma drugs that have already been approved by the FDA and/or EMA, but also on some drugs and methods that are still in process of determining their efficacy and safety.

Among next generation proteasome inhibitors two novel agents, carfilzomib and ixazomib, demonstrated high efficacy in relapsed/refractory settings, and will probably become a backbone of treatment for these patients if not even in newly diagnosed. Carfilzomib showed high efficacy in combination with lenalidomide and dexamethasone in relpased/refractory patients in the ASPIRE trial and gained approval for this group of patients. Further more, in the ENDEAVOR trial, it showed clinical superiority in terms of progression free survival in comparisson with bortezomib. Ixazomib also demonstrated high efficacy in combination with lenalidomide and dexamethasone and was approved for treatment of patients who received at least one prior therapy.

Among the immunomodulatory agents, pomalidomide demonstrated efficacy even in patients refractory to older immunomodulatory drugs and/or bortezomib and is approved for use as single agent or in combination with dexamethasone, in patients who were treated with at least two lines of therapy including lenalidomide and bortezomib and experienced disease progression within 60 days of the most recent treatment.

Extremely exciting and promissing are the data from the trials investigating the efficacy of monoclonal antibodies in treatment of relapsed/refractory myeloma. Two agents from this group are approved in this settting. Daratumumab, anti CD38, with astonishing results regarding progression free survival demonstrated in the interim analysis of the two trials POLLUX and CASTOR. Trials in newly diagnosed patients are still in progress. Second monoclonal antibody, elotuzumab also proved to be very potent antimyeloma agent in combination with lenalidomide and dexamethasone in previously treated patients.

Besides these next generation agents and those menitioned earlier in the text, there are several other drugs that are being studied in multiple myeloma patients. In the proteasome inhibitor class there are two more drugs that are showing promissing results in early phases of clinical trials. These are marizomib and oprozomib. In the monoclonal antibody class indatuximab (anti-CD138) and SAR (SAR650984, another anti-CD38) are being studied. In addition, numerous other agents, some of which are already in use in other lymphoprolipherative diseases, with different mechanisms of action are also being investigated, such as afuresertib (AKT inhibitor), ABT 199 (Bcl-2 inhibitor), ibrutinib (Bruton's tyrosine kinase inhibitor), siltuximab (IL-6 inhibitor) and many others.

Approval of next generation antimyeloma drugs opens many options for treatment of multiple myeloma patients, mainly in the relapsed/refractory settings for now. However, one important question still remains unanswered: which new drug or combination to use?

All of the new drugs in myeloma patients showed benefit for relapsed/refractory myeloma patients. But question will remain wich drug to choose for particular patient. Decision will be mostly made on the availability of the drug, toxicity profile and cost. Regarding costs M. McCarthy showed in article published in BMJ that cost of novel drugs such as carfilzomibe, elotuzumab and ixazomib regiment exceeded cost effectivness thresholds for quality adjusted life year [43].

Since there are no guidlines, the decision has to be made on the case by case principal taking in account above mentioned availability of the drug, toxicity profile and cost as well as patients individual characteristics. We believe that with the use of next generation antimyeloma agents we will be able to acheive better response rates and further improve patients survival in the future.

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