

Incorporating Monoclonal Antibodies Into the Therapy of Multiple Myeloma

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The outcome of patients with multiple myeloma (MM) treated with cytotoxic therapy has not been satisfactory, with a median survival of about 3 years for elderly patients and of about 6 years for younger patients receiving up-front autologous stem-cell transplantation (ASCT).¹ The incorporation of novel drugs, particularly thalidomide, bortezomib, and lenalidomide, has resulted in a significant survival prolongation.^{2,3} However, MM is still an incurable disease with an important shortening in the expected survival.⁴ A number of novel drugs with many different mechanisms of action have been developed and are currently investigated in clinical trials with the hope of further improving the survival of patients with MM.⁵ In this regard, the use of the anti-CS1 humanized monoclonal antibody in combination with bortezomib is described in an article accompanying this editorial. In order to place the findings of this study into clinical context, it will be helpful to briefly review recent progress made in the therapy of this disease.

ASCT is the gold standard as part of the initial therapy in younger patients with MM.¹ With the use of induction regimens based on conventional chemotherapy, the post-transplantation complete remission (CR) rate is between 30% and 35%, the median survival of about 6 years, and the proportion of patients surviving in continued CR beyond 10 years after ASCT is less than 10%.^{6,7} The incorporation of novel drugs into induction therapy has improved the post-transplant CR rate and the progression-free survival (PFS), when compared with the above mentioned results. Thus, triple induction regimens PAD (bortezomib/doxorubicin/dexamethasone) and, particularly, VTD (bortezomib/thalidomide/dexamethasone) result in a post-transplantation CR rate from 43% to 52% with a significant PFS prolongation.^{8,9} Furthermore, post-transplantation consolidation and maintenance with novel agents appears to be an important step forward.^{1,10} Despite the apparent benefit of these treatment approaches incorporating novel drugs, long-term results are required to demonstrate that the improvement is real in comparison with the results achieved in the previous era.¹

Concerning elderly patients, for many years the standard of care has been melphalan and prednisone (MP) or dexamethasone-based regimens, leading to an overall response and CR rates of 50% and 5%, respectively and to a median survival of about 3 years.¹¹ The novel agents thalidomide, bortezomib and lenalidomide have been associated with MP (MPT, MPV or MPR) or dexamethasone, particularly low-dose lenalidomide/dexamethasone resulting in a higher response

rate and PFS in almost all studies and in a significant overall survival prolongation in some of them.¹²⁻¹⁵ The best results have been obtained with MPV which results in approximately 30% immunofixation negative CR and a significant PFS and OS survival prolongation when compared with MP.¹³ However, the incidence of grade 3 and 4 peripheral neuropathy is approximately 13%.¹⁶ A large international trial including over 1,600 patients by the Intergroup Franchophone du Myelome comparing MPT versus lenalidomide and dexamethasone with or without lenalidomide maintenance is ongoing (NIH Clinical Trials identifier NCT00689936). Finally, although the improvement with the incorporation of novel agents is clinically relevant, it is still far from satisfactory. In this regard, the median duration of complete remissions achieved with the above-mentioned combinations is only of 2 years and it unknown if any prolonged remissions (ie, continued CR beyond 10 years from therapy) can be achieved. Therefore, there is also a need for further improvement in the elderly.

The treatment of patients with relapsed or refractory myeloma is a real challenge.⁵ Bortezomib, bortezomib plus pegylated liposomal doxorubicin, or lenalidomide plus dexamethasone are effective regimens and were first approved for patients with relapsed and/or refractory myeloma¹⁷⁻²⁰ (Table 1). However, the duration of response is limited and, unfortunately, all patients will ultimately develop progressive disease. Therefore, there is a need for the development of newer drugs or drug combinations in order to increase not only the response rate but also the durability of responses. In this sense, a new generation of novel drugs is currently being investigated in clinical trials (Table 2). Among them, the most promising are the immunomodulatory drug pomalidomide, the irreversible proteasome inhibitor carfilzomib, which can be active even in refractory patients to bortezomib and that shows an acceptable toxicity profile, and the histone deacetylase inhibitors, particularly SAHA (vorinostat) and LBH 589 (panobinostat). Unfortunately, most of these new drugs have shown limited efficacy when used as single agents.²¹ An interesting approach consists of the addition of a new agent as a second or third drug to a well-established agent or regimen such as bortezomib or lenalidomide/dexamethasone in order to obtain an additive or, hopefully, a synergistic effect.⁵

Despite the availability of an impressive number of new drugs, there is still an unmet need for treatment possibilities in patients with MM. In this regard, a novel anticancer strategy is the use of monoclonal antibodies (MoAb) that act through completely different mechanisms of action. The

Table 1. Pivotal Studies in the Treatment of Relapsed Multiple Myeloma

Regimen	ORR (%)	CR (%)	TTP	OS
Bort v Dex ¹⁷	38 v 18	6 v 1	6.2 v 3.5	80 v 66% at 1 year
Bort + Doxil v Bort ¹⁸	44 v 41	4 v 2	9.3 v 6.5	76 v 65% at 15 months
Len/Dex v Dex ¹⁹	61 v 19.9	14.1 v 0.6	11.1 v 4.7	29.6 v 20.2 months
Len/Dex v Dex ²⁰	60.2 v 24	15.9 v 3.4	11.3 v 4.7	Not reached v 20.6 months

Abbreviations: Bort, bortezomib; CR, complete remission; Dex, dexamethasone; Len, lenalidomide; ORR, overall response rate; OS, overall survival; TTP, time to progression.

paradigm of this approach is the impressive efficacy of the anti-CD20 MoAb, rituximab, in the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukemia.²² Rituximab has played a major role in treating these entities, both in combination with cytotoxic agents and as a single agent in maintenance therapy.²² In MM, MoAb can be directed against a large variety of antigen targets which can be expressed either on myeloma cells or on components of the bone marrow microenvironment (bone marrow stromal cells [BMSCs] or signaling molecules).²³ The main mechanisms of action include antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).²⁴

Unfortunately, rituximab is not effective in MM. This can be due to the fact that less than 20% of the patients show CD20 on plasma cell surface.²⁵ There is the possibility that rituximab could be useful in the subset of patients with translocation t(11;14) with high CD20 expression, but it has not been investigated. Many MoAb are being studied in MM and a number of them have been already incorporated in clinical trials.²⁴ The most promising are summarized in Table 3. One of the most used is the anti-IL6 siltuximab (CNTO 328). IL-6 is a crucial cytokine in MM progression by enhancing antiapoptotic activity²⁶ and it is a potential target for MoAb. Siltuximab increases cytotoxicity of dexamethasone and bortezomib plus dexamethasone combinations.²⁷ It is being investigated in clinical trials, in combination with melphalan, prednisone and bortezomib as up-front therapy in elderly patients as well as a single agent in smoldering multiple myeloma.

Vascular endothelial growth factor (VEGF) facilitates tumor growth by increasing angiogenesis.²⁸ Bevacizumab is a humanized anti-VEGF MoAb which is being studied in MM. In two small phase II trials of relapsed/refractory myeloma approximately 70% of the patients responded to lenalidomide/dexamethasone plus bevacizumab.²⁴ The efficacy of this MoAb in combination with bortezomib

is currently being studied.²⁴ CD40 is highly expressed in both MM cells and BMSCs and its activation by its ligand CD40L induces myeloma cell proliferation.²⁹ The humanized antiCD40 MoAb (SNG-40, dacetuzumab) have been shown to induce cell death by enhancing apoptosis and ADCC in myeloma cell lines and in mouse myeloma models. Dacetuzumab has been studied in combination with lenalidomide and dexamethasone showing some activity in patients previously exposed to lenalidomide.²⁴ Other MoAb under investigation are anti-CD56, anti-CD38 and anti-CD138 (syndecan-1).^{24,30}

In an article accompanying this editorial, Jakubowiak et al³¹ report the results of a phase I escalating-dose clinical trial, combining the anti-CS1 humanized MoAb elotuzumab (HuLuc63) with bortezomib in patients with relapsed and refractory myeloma. CS1 is a cell surface glycoprotein highly expressed on MM cells, and it seems to play an important role in the interaction between MM cells and BMSCs.³² Elotuzumab mainly exerts myeloma cell death by natural killer-mediated ADCC and it also triggers ADCC even against MM cells resistant to conventional and novel agents, including lenalidomide and bortezomib.^{33,34} Thus, a phase I/II study of lenalidomide/dexamethasone plus elotuzumab showed a partial response rate or better of 82%, while a phase II trial showed an 81% response rate including 37% CR or VGPR.

The above mentioned preclinical studies have been the basis for clinical trials combining elotuzumab with bortezomib, as the one by Jakubowiak et al.³¹ Twenty-eight patients with relapsed/refractory MM entered this phase I study of bortezomib with escalating doses of intravenous elotuzumab at 2.5, 5, 10 and 20 mg/kg on days 1 and 11 while bortezomib was given at the usual schedule of initial fixed doses of 1.3 mg/m² on day 1, 4, 8 and 11. Elotuzumab limiting toxicities were not observed during the escalation phase and the maximum-tolerated dose was not reached. The most frequent grade 3 and 4 toxicities were fatigue (14%) and thrombocytopenia (11%). Of note, 20 of the 28 patients (71%)

Table 2. New Generation of Drugs Antimyeloma

Mechanism/Target	Drugs
Proteasome inhibitor	CEP-18770 Marizomib Carfilzomib
Immunomodulatory drug	Pomalidomide
PI3K/AKT/mTOR inhibitor	Temsirolimus Everolimus Perifosine
DNA hypomethylation	5'-azacytidine
Histone deacetylase inhibitor	Vorinostat Panobinostat
Alkylating plus purine analog	Bendamustine
Other	Plitidepsin Zalypsis

Table 3. Monoclonal Antibodies With Potential Clinical Application in Multiple Myeloma

Target	Drug
Surface molecules	
CD20	Rituximab
CD40	Dacetumab
CD56	Lurvatuzumab
CD74	Milatuzumab
CS-1	Elotuzumab
Cytokines	
IL-6	Siltuximab
VEGF	Bevacizumab

Abbreviations: IL-6, interleukin-6; VEGF, vascular endothelial growth factor.

developed a peri-infusional adverse event, but it was grade 3 in only one patient (hypersensitivity reaction), and for this reason a steroid-based premedication regimen was implemented. Interestingly, elotuzumab serum levels were correlated with elotuzumab saturation at CS1 binding sites on bone marrow myeloma cells. Concerning efficacy, a partial response or better was reached in 48% of the patients, including in two of three refractory to bortezomib. The median time to progression was 9.5 months. The authors emphasize their encouraging results with the combination of elotuzumab with bortezomib. With the increasing availability of novel drugs, now incorporating MoAb targeting independent pathways, our objective in MM should be aimed at reaching the best synergistic combinations that result in the greatest clinical benefit for our patients.

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