ISSN 0025-7680

International Symposium
NEW DIRECTIONS IN CANCER MANAGEMENT
Academia Nacional de Medicina
Buenos Aires, 6-8 June 2007

MEDICINA (Buenos Aires) 2007; 67 (Supl. II): 75-78

MYELOMA THERAPIES

A PEAK INTO THE FUTURE

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Abstract Multiple myeloma is a devastating hematologic cancer that is associated with significant comorbidities plaguing the clinical course of the disease. Recent development in myeloma therapeutics has made a positive impact in overall survival of patients. Several new drugs secured approval from the FDA in the last 5 years bringing renewed hope to patients and caregivers. What remains more promising is the combination of these new agents with traditional anti-myeloma therapies that are clinically demonstrating enhanced activity and improvement in the number of patients achieving complete responses. These high rates of clinical responses question the upfront use of high-dose chemotherapy and autologous stem cell transplant. The future of myeloma therapeutics resides in rational and effective combinations that can target both the tumor cell as well as its microenvironment.

key words: myeloma, treatment

Resumen ***Tratamiento del mieloma. Una visión del futuro.*** El mieloma múltiple es una enfermedad hematológica devastadora asociada a una importante comorbilidad a lo largo de su evolución. Sin embargo, el desarrollo de nuevas terapéuticas ha conseguido aumentar la sobrevida de los enfermos. Nuevas drogas aprobadas por la FDA en los últimos cinco años han llevado algo de esperanza a los pacientes y sus familias. Lo que más promete es la combinación de estos nuevos agentes con los tratamientos clásicos, con lo cual se han conseguido remisiones completas. Se discute el uso de altas dosis de quimioterapia y del trasplante autólogo de células progenitoras (*stem cells*). El futuro del tratamiento del mieloma dependerá de combinaciones efectivas para atacar la célula tumoral y también influir sobre el microambiente.

Palabras clave: mieloma, tratamiento

Multiple myeloma remains an incurable blood cancer of plasma cell origin. It is characterized by infiltration of the bone marrow by malignant plasma cells, aberrant immunoglobulin production, renal dysfunction, lytic bone disease and overall immune immunosuppression[1]. Standard therapies have limited effectiveness; all patients eventually relapse and die of refractory disease with a median survival of 3.5 years[2]. There is urgent need for new drug development in myeloma.

Improved understanding into the pathogenesis of the malignant myeloma cell especially its interaction with the microenvironmental elements is directing efforts in new drug development and novel therapeutic approaches. This manuscript will overview some of the novel therapies that are under development for patients with multiple myeloma and reflect on the future of myeloma therapeutics in context with rapidly developing novel agents.

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Biology of malignant myeloma cell

Recent insights in myeloma biology demonstrates the critical role played by several pro-survival pathways. For example, induction of Raf/MEK pathway supports myeloma cell proliferation while resistance to chemotherapy is reported to be associated with upregulation of the PI3/Akt pathway[3]. Modulation of these pathways is mediated through a complex network of cytokines such as IL-6, TNF-α and VEGF[4, 5]. While the conventional approach in treating myeloma has focused on cytotoxic drugs, understanding myeloma biology has resulted in the exploitation of these pathways as potential targets for drug development (Fig. 1)[6]. Results from clinical studies with thalidomide (immunomodulatory agent)[7-10] and bortezomib (proteasome inhibitor)[11-13] show that this approach is equally effective and is independent of resistance to conventional cytotoxic agents. For example, bortezomib down regulates IL-6 transcription through inhibition of NFκB while thalidomide decreases the stromal cell production of pro-survival cytokines TNF-α and VEGF via down regulation of intercellular adhesion molecule

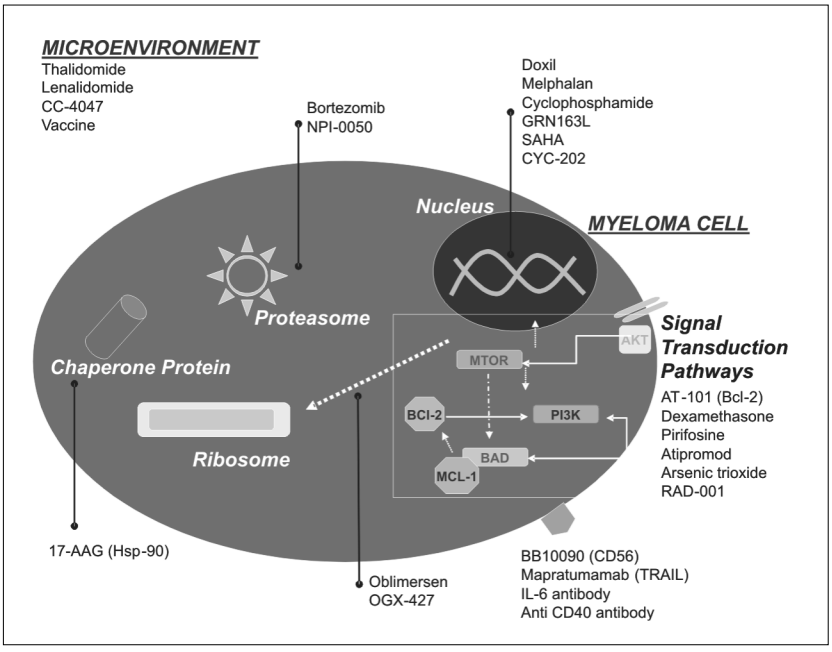

Fig. 1.– Schematic representation of drugs and their site of action in multiple myeloma cell or its microenvironment.

(ICAM) mediated cell signaling.[14] These new agents have changed the treatment paradigm in multiple myeloma and have resulted in promising combination treatment regimens as well as paved the way for investigation of new drugs.

Myeloma therapeutics

Until recently the most common therapeutic approach for newly diagnosed myeloma patients was to initiate dexamethasone based induction cytoreductive therapy such as the VAD or the DT regimen. In younger (age ≤ 65 years) patients this was followed by high-dose chemotherapy with melphalan and autologous stem cell transplantation. Despite achieving high overall response rate (ORR) the complete response (CR) rate with this approach remained low (20-40% in various series) and more importantly none of the patients were cured. Singhal et al[12] in 1996 reported thalidomide ability to induce clinical remission in myeloma patients with relapsed or refractory disease. Although the mechanistic insight of thalidomide action remains elusive, this discovery changed the treatment paradigm of myeloma therapeutics. Further work done by various investigators demonstrated that thalidomide modulates the myeloma cell microenvironment through down regulation of various prosurvival cytokines (e.g., VEGF, IL-6 and TNF-α) as well as modulates the crosstalk between the myeloma cells and the bone marrow stromal cells resulting in survival disadvantage of the malignant myeloma cells.

TABLE 1.– *Various treatment regimens investigated as primary therapy for multiple myeloma patients*

Regimen	OR	CR
Bortezomib	40	10
Bortezomib/Dexamethasone	88	18
Lenalidomide/Dexamethasone	90	24
Bortezomib/PLD	79	28
Bortezomib/Thalidomide	82	31
PDL/Dexamethasone/Thalidomide	98	34
Bortezomib/doxorubicin/dexamethasone	95	26
Bortezomib/PLD/Dexamethasone	89	32
Melphalan/Prednisone - Thalidomide	76	28
Melphalan/Prednisone - Lenalidomide	81	48
Melphalan/Prednisone - Bortezomib	86	43

Abbreviations: PLD; pegylated liposomal doxorubicin.

Identification of the role played by various signal transduction pathways in myeloma pathogenesis further opened the avenues for future drug development. As a result new drugs and novel combination regimens (Tables 1 and 2) have recently revitalized the field of myeloma therapeutics with higher ORR and CR rates.

Immunomodulating agents: Thalidomide and its analogs have become an integral part of myeloma therapy. Several clinical trials investigated the role of thalidomide in combination with dexamethasone as initial myeloma

TABLE 2.– *New therapeutic agents and novel combination in clinical investigation for patients with multiple myeloma*

New Agents	Target	Development phase
BB-10090	Anti-CD56	Phase I
17-AAG	Hsp-90 inhibitor	Phase I
Atipromod	MAPK – inhibitor	Phase I
GRN-163L	Telomerase inhibitor	Phase I
NPI-0050	Proteasome inhibitor	Phase I
Perifosine	MAPK-inhibitor	Phase I
Novel Combinations		**Development phase**
Bortezomib + Lenalidomide		Phase I
Bortezomib + 17-AAG		Phase I
Bortezomib + Mapratumamab		Phase II
Bortezomib + PLD + Thalidomide		Phase II
Bortezomib + PLD + Lenalidomide		Phase I/II
Cyclophosphamide + Prednisone + Lenalidomide		Phase II

Abbreviation: PLD; pegylated liposomal doxorubicin.

therapy. Overall these studies established dexamethasone/thalidomide as an effective and well tolerated primary myeloma therapy with an expected response rate of 60-65% though the incidence of CR rates remained low (< 10%). Recently, Palumbo et al reported that addition of thalidomide to the MP regimen (melphalan/prednisone) resulted in significant improvement of responses (ORR 80% vs. 47%; CR/nCR 28% vs. 7%) as well as in median progression free survival (33 vs. 14 months; $p < 0.001$)[15]. Interestingly, the MPT combination also proved to be more potent than high-dose chemotherapy and autologous stem cell transplant when compared in a randomized study. The median progression free and overall survival in this study for MPT and transplant was 29.5 and 19 months ($p<0.001$) and >56 months and 38.6 months ($p<0.014$). These studies undoubtedly establish the beneficial role of thalidomide in combination with standard chemotherapy based regimen in elderly myeloma patients.

Lenalidomide a newer analog of thalidomide with improved toxicity profile and *in vitro* evaluation demonstrating higher potency in down regulation of tumor supporting cytokines such as VEGF and TNF-α demonstrated encouraging single agent activity in myeloma patients who had previously failed therapy[16]. In a phase I/II clinical trial While, Palumbo et al.[15] substituted lenalidomide for thalidomide in combination with melphalan/prednisone and demonstrated clinical benefit in 100% of the patients with a CR rate of 24% and a partial response (PR) of 57%, Rajkumar et al reported 91% ORR when lenalidomide was combined with dexamethasone in treatment naïve patients.[17]

Collectively these studies highlight the important role played by the IMiD molecules in myeloma therapy and the evolution of combination regimen with higher ORR and CR rates.

Proteasome inhibitor therapy: Bortezomib is a first in class proteasome inhibitor approved for the treatment of myeloma patients[11]. Treatment with single agent bortezomib results in ORR and CR rate of 40% and 10% respectively, combination with other antimyeloma agents results in higher ORR and CR rates ranging from 80-95% and 18-48% respectively (Table 1). Orlowski et al was the first to report that pegylated liposomal doxorubicin (PLD) enhances the clinical activity of bortezomib in myeloma patients[18]. In a phase II clinical trial conducted by CALGB (Cancer and Leukemia Group B) bortezomib/PLD combi-nation resulted in an ORR and CR rate of 79% and 28%. The clinical importance of this regimen resides in the fact that this is a steroid free treatment regimen with equivalent efficacy. We combined bortezomib/PLD with thalidomide and demonstrated high efficacy in relapsed/refractory myeloma patients with an OR and CR rate of 55% and 22%[19]. Currently this triple combination is investigated as a frontline option for myeloma patients at Roswell Park Cancer Institute.

Despite encouraging results with novel new combinations especially higher percentage of patients achieving complete response without even utilizing high-dose chemotherapy and autologous transplant, myeloma

remains an incurable disease with eventually all patients developing disease relapse and drug resistance. Thus continued effort in development of new drugs with varied mechanisms of action as well as rationale combination with existing drugs is essential.

Novel agents

Improved understanding in the biology of multiple myeloma has allowed a more focused effort in development of new drugs for myeloma treatment. Some of the more promising ones in early clinical evaluation are highlighted here (Table 2).

17-AAG (Tanespimycin®) is a heat shock protein 90 inhibitor that is currently investigated in relapsed or refractory myeloma patients. Two ongoing phase I studies are investigating the maximum tolerated dose of 17-AAG either alone or in combination with bortezomib. Although single agent 17-AAG is only showing modest anti-myeloma activity, interesting observations are reported from the clinical study investigating 17-AAG in combination with bortezomib. Among the 30 patients so far enrolled the overall response rate is 57%. Interestingly, clinical activity is noted even in patients resistant to bortezomib[20].

BB-10090 BB-10901 is a humanized monoclonal antibody that binds with high affinity to CD56 and is covalently linked to a novel cytotoxic maytansinoid DM1. Once bound to CD56, the conjugate is internalized and releases DM1. Around 70% of the patients with multiple myeloma express CD56. Preliminary result from an ongoing phase I clinical trails is showing anti-myeloma effects of this agent. Future clinical trials may incorporate this antibody with established anti-myeloma therapies[21].

NPI-0050 is a new proteasome inhibitor that has demonstrated potent proapoptotic activity in human myeloma cell lines as well as primary tumor cells obtained from patients resistant to bortezomib. This compound has initiated its phase I, dose finding journey. While the preclinical data is exciting results of this clinical trial will determine its future role in myeloma therapeutics[22].

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