New developments and treatment in multiple myeloma: new drugs in the treatment of multiple myeloma

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Introduction

Multiple myeloma (MM) remains a fatal disease: median overall survival does not exceed 3 years with conventional chemotherapy approaches. Melphalan and prednisone (MP) chemotherapy was introduced in the 1960s, and has not been significantly modified since [1]. Melphalan and prednisone induces a response in about 50–60% of MM patients: disappearance of M component by electrophoresis occurs in about 3% of patients.

A dose–response relationship in MM has been clearly shown by McElwain et al. [2]: high-dose melphalan without any stem cell support induces high rates of complete response in patients refractory to conventional melphalan doses. Barlogie et al. [3] showed that the hematological toxicity induced by high-dose melphalan was reduced if followed by the autologous bone marrow transplantation. The availability of hematopoietic growth factors allowed the mobilization from the bone marrow into the circulation of large amounts of peripheral blood progenitor cells. These cells can be collected and re-infused after treatment with high-dose melphalan, significantly accelerating hemopoietic recovery. The percentage of complete remissions has increased ten-fold from 1–3% to 30–50%. Remission duration has been prolonged by at least 10 months from a median duration of about 18 to 30 months. Overall survival has improved from about 20 to 60 months. Despite these therapeutic improvements the disease tends to recur in all patients: molecular evaluations of minimal residual disease are able to detect neoplastic myeloma cells in virtually all patients after a single or a double autologous transplant [4]. The development of resistance to chemotherapy determines disease progression which is the major cause of death.

A cure in MM appears to be achievable only by allogeneic transplantation: about 50% of transplanted patients become molecularly negative and remain in complete remission (CR) for several years [5]. Moreover, even after non-myeloablative transplantation, molecular CR has been observed as a proof of principle of the strong graft-versus-myeloma effect evoked with this novel procedure (personal observation). However, a few MM patients can tolerate allogeneic procedures. Thus, to improve outcome, it is necessary to search for new drugs or new strategies with old drugs.

Prototypes of these old/new drugs are thalidomide (THAL) and proteasome inhibitors. THAL was introduced in 1999 by the Little Rock group as a salvage therapy for refractory patients [6]. It was immediately recognized as highly active by the scientific community, and eventually widely used. The exact mechanism of action of THAL is still largely unknown, and the ongoing biological studies will clarify this crucial point. Proteasome inhibitors have been described in 1999 as effective anti-tumor drugs in preclinical studies [7]. Many aspects of their mechanism of action are known, including their interplay with inhibitor/activator proteins, the genes that are regulated and finally, their effect on cell growth and apoptosis of normal and neoplastic cells [8]. The scientific community is waiting to know the results of the preliminary phase I–II studies. Thus, the new/old drugs are following different pathways: from the bench to the clinic, or in the opposite direction from the clinic to the bench.

The new/old drugs recently introduced and tested in large phase I–II trials are briefly reviewed here. They include THAL, proteasome inhibitors and bisphosphonates. Several other interesting molecules are currently being tested, but they are not expected to be available in the near future.

Thalidomide

Thalidomide has been banned from widespread clinical use since 1962 because of severe teratogenicity. It was reintroduced as an effective oral agent in the management of several disease states, including erythema nodosum leprosum, and more recently malignancies including MM. Thalidomide blocks the ability of vascular endothelial growth factor (VEGF) and fibroblast growth factor β (β-FGF) to stimulate neovascularization of bone marrow. Thalidomide directly inhibits the growth and survival of myeloma cells, modulates some adhesion molecules, inhibits tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6) secretion. However, the exact mechanism of action of THAL in MM remains to be determined.

A phase II trial of THAL in refractory MM was initiated using a dose schedule that escalated from 200 mg/day to 800 mg/day [9]. More than two thirds of patients had cytogenetic abnormalities and more than half had received at least two cycles of high-dose therapy. A paraprotein reduction of at
least 25% was noted in 37% of patients and 14% had either a CR or a near CR. No treatment-related mortality was observed. With a median follow-up of almost 2 years, the 2-year event-free survival (EFS) and overall survival (OS) estimates were 15% and 60%, respectively. Thus, THAL appeared to be highly effective in refractory and recurrent myeloma. The absence of myelosuppressive toxicity suggests that thalidomide is an ideal agent to be used in combination with cytotoxic agents and dexamethasone (DEX).

We recently evaluated the efficacy of the combination of THAL plus DEX: MM patients were treated with low-dose THAL (100 mg/day) continuously and DEX 40 mg, days 1–4, every month [10]. From June 1999 to August 2000, 77 patients (median age 65 years) who had relapsed or were refractory to chemotherapy were treated. Fourteen patients (18%) showed a myeloma protein reduction of 75–100%, 18 patients (23%) showed a reduction of 50–75%, 19 patients (25%) a response of 25–50% and 26 patients (34%) a response of <25% or disease progression (Table 1). After a median follow-up of 8 months, median progression-free survival was 12 months (Figure 1). THAL was well tolerated. Constipation (12%) and sedation (6%) were mild. Tingling or numbness were present in 17% of patients. Discontinuation of treatment was required in 10% of patients. Other studies have also proven the efficacy of low-dose THAL plus DEX in refractory MM patients [11].

Thalidomide is certainly a new tool for refractory patients; however, its superiority over conventional chemotherapy (CC) has not yet been proven. To address this issue, from March 1999 to December 2001, 120 patients (median age 63) that relapsed or were refractory to chemotherapy were treated with THAL 100 mg/day in continuous and DEX 40 mg, days 1–4, every month. Their clinical outcome was compared with a control group of 120 pair mates (median age 60) selected from relapsed or refractory patients treated with CC and matched for serum β2-microglobulin levels and Durie and Salmon clinical stage. Response to treatment, and event-free survival were similar in patients treated with THAL plus DEX and CC, but survival was prolonged in the THAL plus DEX group. This benefit was particularly evident when survival analysis was calculated from progression occurring after THAL–DEX or CC salvage. It can be argued that THAL is a non-myelosuppressive drug allowing further chemotherapy delivery at the occurrence of a second relapse.

Long-term toxicity is still an open question. In pregnant women, birth defects are well known. In men, the oral administration of THAL induces detectable levels in semen [12]. Since the threshold dose for birth defects is unknown, barrier contraception is mandatory for both men and women taking THAL. Increased risk of deep-vein thrombosis was observed in patients receiving THAL in combination with multi-agent chemotherapy and dexamethasone [13]. In our experience, the combination THAL–DEX did not increase the incidence of deep-vein thrombosis, which was identical to that observed in the control group.

Neurotoxicity is the main complaint. It is dose-dependent and time-dependent, and it is the major cause of drug reduction/discontinuation.

Several trials are currently underway to determine the clinical benefit of adding THAL up front, as maintenance treatment or at relapse in various combinations with chemotherapy and glucocorticoids. Even the optimal dose is still to be defined: a THAL dose–response effect was observed, but only 55% of patients received the intended maximal daily dose of 800 mg [14]. The results of these controlled trials will clarify its effect on event-free and overall survival, the long-term toxicity and eventually the best timing of application.

### Proteasome inhibitors

The proteasome regulates protein turnover in eukaryotic cells. The ubiquitin-mediated proteasome degradative pathway regulates a large repertoire of intracellular proteins that finally control cell cycle, tumor growth and survival. In recent years, selective inhibitors of the proteasome have been used in cell cultures to define the anti-tumor potential of these compounds. PS-341, a dipeptide boronic acid, induced *in vitro* tumor cell apoptosis and *in vivo* reduced significantly decreased tumor

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**Table 1. Thalidomide plus dexamethasone: response**

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
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<tbody>
<tr>
<td>75–100%</td>
<td>18%</td>
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<tr>
<td>50–75%</td>
<td>23%</td>
</tr>
<tr>
<td>25–50%</td>
<td>25%</td>
</tr>
<tr>
<td>No response*</td>
<td>34%</td>
</tr>
</tbody>
</table>

*Response <25%, stable disease or progression.*

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**Figure 1. Thalidomide plus dexamethasone: progression-free survival.**
burden in mice bearing PC-3 tumor [7]. Moreover, a synergistic effect with dexamethasone has been described.

NF-\(\kappa B\) has been reported to play a growth and anti-apoptotic role in multiple myeloma [15]. Myeloma cell adhesion to stromal cells induces a NF-\(\kappa B\) dependent up-regulated transcription of IL-6, a growth and anti-apoptotic factor. NF-\(\kappa B\) is inhibited by the association with I\(\kappa B\) inhibitors: the phosphorylation of the I\(\kappa B\) inhibitor induces their degradation by 26S proteasome. PS-1145 specifically inhibits the phosphorylation of I\(\kappa B\) inhibitor, preventing their degradation [16]. These studies suggest the potential utility of new therapeutic approaches targeting NF-\(\kappa B\) in MM myeloma using proteasome inhibitors.

The safety profile of phase I trials of PS-341 are encouraging, and several large phase I–II trials are underway in refractory myeloma.

**Bisphosphonates**

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption. They accumulate in the mineralized bone matrix, making it more resistant to dissolution by osteoclasts. Moreover, they directly inhibit the osteolytic activity of osteoclasts and reduce their survival. Thus, they represent the treatment of choice for hypercalcemia determined by osteolytic lesions [17].

Pamidronate, a second generation amino-bisphosphonate, has been evaluated in a randomized, double-blind trial [18]. Bone pain and analgesic requirement were significantly reduced in the pamidronate group. Total number of skeletal events and episodes of hypercalcemia were reduced by half. Survival was also prolonged in poor prognosis patients who failed to respond to first-line chemotherapy before entering the trial. Thus, bisphosphonates are considered as a new form of treatment for MM.

A more potent third-generation of bisphosphonates, such as zoledronate, has proven superior to pamidronate in the treatment of hypercalcemia and skeletal metastasis [17, 19]. However, preclinical studies have demonstrated a direct anti-tumor activity in human breast, prostate and myeloma cell lines [20]. Large clinical studies are ongoing on breast cancer, prostate cancer [21] and MM, and the results are expected to be presented this year.

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**References**


