

Recent Advances of Thalidomide in the Treatment of Multiple Myeloma

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Multiple Myeloma (MM) is a chemoresistant malignancy and for decades, the only active drugs were alkylating agents and high-dose corticosteroids. The introduction of novel agents (Thalidomide, Bortezomib and Lenalidomide) is changing the management of MM patients both for frontline therapy and at relapse. These agents have a different mode of action and can act not only on the myeloma cells but also on the microenvironment which is necessary for tumor cell survival and proliferation. In vitro experiments have shown possible synergy with dexamethasone or chemotherapeutic agents. They are active even in heavily pretreated patients and offer new possibilities for relapsed/refractory MM.

Thalidomide

Thalidomide as a single agent

Thalidomide is administered orally. Due to its teratogenicity, it is prescribed according to risk-management programs to avoid exposure of women with child-bearing potential.

Thalidomide was introduced in the treatment of relapsed MM by the Arkansas group (1). Following the results of this pioneer work, a large number of Phase II studies were reported and were summarized in a comprehensive review (42 studies, 1674 patients) (2). From this experience, the following conclusions are possible (2-5).

- The response rate is approximately 45% including 30% partial remissions (PR)
- Complete remission (CR) are rare in heavily pretreated patients but possible

- The onset of response is rapid (less than 2 months) and maximal response is achieved within 6 months
- One-year event-free survival (EFS) is about 35% and median overall survival (OS) is 14 months
- Prognostic factors with thalidomide treatment are the same as with conventional chemotherapy and include tumor burden markers and cytogenetic abnormalities
- Thalidomide can be prescribed in patients with renal dysfunction
- Myelosuppression is very rare
- The incidence and severity of side effects is related to the daily dosage. With the doses initially used (400 mg/day) the most frequent toxicities were constipation, somnolence, fatigue and peripheral neuropathy.

Peripheral neuropathy causes numbness, paresthesia and even pain in legs and arms. The overall incidence of peripheral neuropathy is 30% with 10% grade ≥ 3 , but is related to cumulated dose and is up to 75% in patients treated more than one year (6). Since there is no effective prophylaxis and treatment, the drug should be discontinued in case of peripheral neuropathy signs or symptoms (3-5).

Currently the daily doses of Thalidomide have been reduced to 100-200 mg/day.

Thalidomide in combination

The combination of Thalidomide plus Dexamethasone has been developed with the objectives of increasing the efficacy and of reducing the daily dose and the toxicity of Thalidomide (6-8). Although

no randomized study comparing Thalidomide and Thalidomide/Dexamethasone (TD) has been performed, TD is considered more effective than Thalidomide alone (approximately 45% response rate) and superior to conventional chemotherapy as treatment of first relapse (9). Since Thalidomide is not myelotoxic, combinations with chemotherapy have also been evaluated in Phase II trials with response rates ranging from 36% to 73%.

While combinations of Thalidomide with Dexamethasone or chemotherapy alone appear to be more active, they are more toxic with a higher incidence of infectious complications. Most importantly they induce an unexpected complication, deep vein thrombosis. While with Thalidomide alone the incidence of deep vein thrombosis is < 5% as with any treatment of MM, with TD the incidence is 10-15% and with chemotherapy (specially anthracyclines) it increases up to 30% (10, 11). This complication usually occurs during the first 3 months of treatment and is more frequent in newly diagnosed patients and in patients with a high tumor burden. The optimal prophylaxis is not yet known and oral anticoagulant, low molecular weight heparin and low-dose aspirin are currently evaluated (3).

Bortezomib

Bortezomib is the first in class proteasome inhibitor. In MM it is active not only on the myeloma cell but also on the microenvironment which is necessary for tumor cell proliferation and survival. It is administered IV at a dose of 1.3 mg/m² on days 1, 4, 8, 11 in 21 days cycles. Two Phase II studies have shown that in heavily pretreated patients, response rate with Bortezomib as a single agent is 25-30% and can be increased by the addition of Dexamethasone (12, 13). Following these studies, the drug has been approved in the US and Europe. The large randomised Phase III trial APEX has demonstrated that Bortezomib is superior to Dexamethasone in relapsed MM, in terms of response rate (including CR), time to progression and OS (14). The onset of response is rapid, usually within 2 cycles but the maximal response can be achieved after up to 8 cycles. A subgroup analysis on patients having received one line of treatment confirmed the superiority of Bortezomib compared to Dexamethasone as treatment of first relapse (15). Based on these Phase II-III studies the toxicity profile is well defined. The most frequent side effects are gastrointestinal symptoms (diarrhea or constipation) and fatigue but they are usually

mild. The drug is not myelotoxic but can induce up to 60% decrease of the platelet count (16). This thrombocytopenia is rapidly reversible usually before the following cycle. Peripheral neuropathy is observed in 30-40% of cases (grade \geq 3 in 10-15%). Signs and symptoms are reversible in 2/3 of cases after dose reduction or drug discontinuation (17). Bortezomib appears to be as effective in older patients and in patients with poor risk disease (18, 19). It can be prescribed safely in patients with renal failure, even in patients on dialysis (20, 21). Based on preclinical studies and on the drug toxicity profile, a number of Phase II studies have evaluated Bortezomib in combination with either Dexamethasone or with chemotherapy.

Lenalidomide

Lenalidomide is a Thalidomide analog which appears to be more potent in vitro. It is not teratogenic in animal models but most importantly, after the Phase I study it became apparent that the toxicity profile of Lenalidomide was completely different (22). Constipation, somnolence, fatigue and peripheral neuropathy that are frequent adverse events with Thalidomide, were not observed. The most frequent side effect was myelosuppression mostly after 28 days of treatment. In Phase II trials the drug was given orally for 21 consecutive days. The response rate in heavily pretreated patients was 25% and was increased by the addition of Dexamethasone (23). Two large randomized trials were then conducted in the US and in Europe (24, 25). They both compared Lenalidomide (25 mg/day on 21 consecutive days) plus high-dose Dexamethasone versus Dexamethasone. They both showed the superiority of the combination in terms of response rate (including CR), time to progression and OS. Based on these studies, the drug was approved by FDA in 2006 and the European approval is pending. However, like with Thalidomide, the combination of Lenalidomide with Dexamethasone induces deep vein thrombosis and justify prophylactic treatment at least with low-dose aspirin. The treatment should be used with caution in patients with renal failure due to a higher myelotoxicity (specially thrombocytopenia) in patients with less than 50 ml/min creatinine clearance. Lenalidomide is currently tested upfront in combination with dexamethasone or with chemotherapy.

Combination of novel agents

Since the toxicity profiled of these three agents is different, it appeared logical to combine them

with the objective of increasing efficacy. The combination of Thalidomide or Lenalidomide with Bortezomib was the most attractive, due to a possible synergy of agents having different mode of actions. Thalidomide and Bortezomib have been combined with either Dexamethasone (VTD) or with Melphalan Prednisone (VMPT) with very encouraging results and an acceptable toxicity (26, 27). The combination Bortezomib-Lenalidomide is currently tested (28).

Role of Stem Cell Transplantation at first relapse

Autologous Stem Cell Transplantation (ASCT) is currently considered the standard of care for frontline therapy in patients up to 65 years of age. However ASCT is also a useful salvage treatment in chemosensitive or untreated relapses (29). When comparing early ASCT, and ASCT when conventional chemotherapy fails (late ASCT) there is no difference in OS although time to progression is longer with early ASCT (30). If late ASCT is considered it should be useful to collect stem cells early (31) since the hematopoietic quality of grafts is often decreased by previous chemotherapy specially alkylating agents (32). When ASCT has been performed upfront, a second ASCT is justified if the duration of first remission has been > 2 years.

Allogeneic SCT is probably the only treatment that can induce long term clinical and molecular remissions. However standard myeloablative regimens prior to allogeneic SCT have been almost abandoned specially for relapsed MM, due to a high transplant-related mortality (up to 50%) (33).

With reduced-intensity conditioning allogeneic SCT, transplant-related mortality is reduced, even in relapsed MM (20-25% at 1 year) (34). However the risk of relapse is higher than with standard allogeneic SCT, specially in chemoresistant disease or when the tumor burden is high (35). Current strategy aims at reducing the tumor burden first, for instance with high-dose Melphalan followed by ASCT, and then to exploit the graft-versus myeloma effect of donor lymphoid cells. This strategy is mostly proposed for first line treatment in patients with an HLA-identical donor (36) but can also be offered at first relapse if CR or VGPR has been achieved with salvage therapy.

Therapeutic strategy

With the introduction of novel agents, CR achievement is possible in relapsed MM. In the

large randomized studies testing Bortezomib and Lenalidomide, the progression-free survival (PFS) and OS increase was associated to a CR rate increase, as compared to the control arms (12, 24, 25). In the APEX trial, PFS was 12 months for patients in CR versus 8 months for patients with only PR (37). Therefore, as for frontline therapy, the objective of first relapse treatment should be to achieve the best possible response.

With this objective, it is logical to use novel agents for first relapse treatment since they are effective even in heavily pretreated patients. Although no randomized study has compared Thalidomide, Bortezomib or Lenalidomide given as single agents to combinations, they are usually administered in combination at least with dexamethasone (TD, VD or RD). Out of a clinical trial, the choice depends on a variety of parameters including age, previous treatment, prior toxicities, availability of novel agents (which is not the same all over the world). There are special situations in which the choice is easier.

For instance if Thalidomide has been used for frontline therapy it is better to use Bortezomib or Lenalidomide to avoid the risk of peripheral neuropathy related to cumulative doses of Thalidomide. In patients with renal failure, Bortezomib is the treatment of choice while in patients with peripheral neuropathy, Lenalidomide should be preferred. Fulminant relapses or poor risk cytogenetics should be treated with combinations including Bortezomib or Lenalidomide.

The optimal duration of salvage treatment is unknown. In order to reduce the risk of toxicity and of resistant clones selection, treatment could be stopped 3 months after best result is achieved. In younger patients (< 65 years) ACSH can be considered in sensitive relapses if stem cells are available. Reduced intensity conditioning allogeneic SCT is possible in patients who achieve CR with salvage treatment.

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