Advances in biology and treatment of multiple myeloma

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Biology

A multistep process of ordered genetic changes leads to the development of overt multiple myeloma. This includes changes in the bone marrow microenvironment supporting tumor growth and failure of the immune system to control the disease.

Primary translocations are mediated mainly by errors in immunoglobulin (Ig) heavy-chain switch recombination, but are sometimes also caused by errors in somatic hypermutation during plasma cell generation in germinal centers. The primary translocation involves predominantly the heavy chain locus on chromosome 14 and five partner chromosomes, namely 4p16, 6p21, 11q13, 16q23 and 20q11. This leads to the association of an putative oncogene with the Ig enhancer, which results in the activation of the oncogene [1, 2]. Despite the promiscuity of translocation partners, most Ig translocations involve just three groups of genes (cyclins, MMSET and FGFR3, and c-Maf and mafB). These translocations identify distinct subtypes of myeloma with important prognostic implications. The primary translocation is believed to induce karyotypic instability facilitating somatic mutations and secondary Ig gene translocations involving c-myc and others.

After the transforming event, plasmablasts start expressing various adhesion molecules, leave the germinal center, enter the circulation and home to the bone marrow, where they engage in close interactions between bone marrow stroma cells and fibronectin (Figure 1) [3]. This results in the production of various cytokines that inhibit apoptosis, enhance proliferation and differentiation of myeloma cells, recruit osteoclasts from mononuclear precursor cells and induce them to greatly increased activity.

Diagnosis

Diagnosis of multiple myeloma is based on the presence of a monoclonal protein, bone manifestations and on bone marrow plasma cell infiltration. Patients with multiple myeloma must be distinguished from those with monoclonal gammopathy of unknown significance (<10% bone marrow plasma cell infiltration, low M-component levels (<3 g/dl) and no osteolytic bone lesions) and those with amyloidosis or other lymphoproliferative disorders with paraproteinemia. Recent guidelines recommend differentiating between symptomatic and asymptomatic myeloma. Symptomatic patients present with one or more of the CRAB criteria (hypercalcemia, renal failure, anemia, bone lesions) and need active treatment, in contrast to asymptomatic patients, which should be followed only [4].

Symptoms

Pain in lumbar spine, often mistaken as harmless consequence of common spondylarthrosis, is the most frequent symptom encountered in patients with myeloma.

Weakness, fatigue and loss of energy as the result of the underlying malignancy and frequently also of concomitant anemia are seen in many patients.

A significant proportion of patients present with an increased frequency of infections, mainly with encapsulated bacteria due to suppressed synthesis of normal immunoglobulins and to cellular immunodeficiency.

Renal insufficiency is the leading manifestation of myeloma in ~5% of patients, but is more common with long standing disease.

Similarly, hypercalcemia rarely is encountered as a leading symptom at diagnosis, but is more frequent in far-advanced progressive disease.

Spinal cord or nerve root compression with paraplegia is an emergency necessitating immediate intervention. Surgical removal of the tumor mass is the preferred approach provided this will not result in instability of the vertebral column; otherwise local radiotherapy and high-dose dexamethasone should be administered.

Hyperviscosity is much rarer nowadays, and is mostly seen in patients with IgA paraproteins (owing to their tendency to form aggregates) and in Waldenström’s macroglobulinemia.

Staging

Traditional staging is performed according to the Durie–Salmon staging system and patients are assigned to stages I to III and subclassified as those without (subtype A) and with (subtype B) renal impairment (creatinine >2 mg/dl). A group of international investigators recently compiled data from 10 750 patients and evaluated various clinical and laboratory parameters and their relevance for prognosis [5]. These efforts resulted in the creation of the International Staging System (ISS), (Table 1), which provides two advantages over the Durie–Salmon system. The ISS relies on widely available
laboratory parameters and allocates patients to equally sized patients groups with markedly different prognoses. In contrast, the Durie–Salmon system depends on the subjective evaluation of the extent of bone involvement and usually results in an imbalanced distribution of patients (more patients are categorized as stage III than as stage I or II).

**Prognosis**

Prognosis of multiple myeloma depends on both biological features of the myeloma clone and patient-specific features. Previously, lactate dehydrogenase, $\beta_2$-microglobulin, labeling index, bone marrow plasma cell infiltration and morphologic features of myeloma cells were considered as the most important prognostically relevant biological parameters. Recent findings indicate the superior importance of cytogenetic parameters. Patients with deletion of chromosome 13 and hypodiploidy have a poor survival [6]. Likewise, survival is short in patients with translocation 4;14, whereas outcome is superior in those with translocation 11;14 and those with hyperdiploidy [7].

Patient inherent parameters related to prognosis are age, renal impairment, anemia and co-morbidity.

**Selection of therapy**

Patients with asymptomatic myeloma should not be started on therapy but be monitored carefully only. In contrast, treatment should immediately be installed in those with symptoms or at threat for complications owing to myeloma.

High-dose chemotherapy with autologous transplantation is the treatment of choice for patients fit for this procedure. These are patients younger than 65 years old, or older but physiologically qualified for transplantation. All other patients are candidates for conventional chemotherapy, single-agent dexamethasone treatment or new treatments such as thalidomide and bortezomib with or without combination with other drugs.

### Table 1. The International Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Median survival (months)</th>
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<tbody>
<tr>
<td>I</td>
<td>Albumin $\geq$ 3.5 g/dl and $\beta_2$-microglobulin $\leq$ 3.5 mg/dl</td>
<td>60</td>
</tr>
<tr>
<td>II</td>
<td>Albumin $&lt;3.5$ g/dl and $\beta_2$-microglobulin $&lt;3.5$ mg/dl or $\beta_2$-microglobulin $3.5-5.5$ mg/dl</td>
<td>42</td>
</tr>
<tr>
<td>III</td>
<td>$\beta_2$-Microglobulin $\geq$ 5.5 mg/dl</td>
<td>27</td>
</tr>
</tbody>
</table>
**Conventional treatment**

Patients with good prognostic features may be started on single-agent dexamethasone treatment, which will induce remission in \( \sim 40\% \) of cases. Patients with poor prognosis as defined by high baseline \( \beta_2 \)-microglobulin and or deletion of chromosome 13 should be started on a more aggressive treatment, such as VAD (vincristine, adriamycin, dexamethasone), or the somewhat less aggressive melphalan or melphalan–prednisone. An algorithm of treatment selection is shown in Figure 2.

An upcoming alternative for first-line treatment is thalidomide–dexamethasone [8] or thalidomide–melphalan–prednisone [9]; the former regimen induces remissions in 60–70\% and the latter in 70–80\% of previously untreated patients. Bortezomib has been shown to be effective as treatment in patients relapsing or refractory to multiple previous treatments [10]. Preliminary data show a high efficacy of single-agent bortezomib or bortezomib in combination (overall response rate with bortezomib–doxorubicin–dexamethasone 93\%) (Table 2).

**Autologous transplantation**

Autologous transplantation is the treatment of choice in patients younger than 65 years old, or older, but fit for this procedure. Five prospective randomized trials comparing autologous stem cell transplantation with conventional chemotherapy have been published so far (Table 3). The French IFM 90 [19], the British MRC [21] and the Italian MMSG trial [22] have shown a statistical significant prolongation of overall survival with stem cell transplantation. Most other trials demonstrated significantly higher response rates and longer time to progression, but only a tendency for improved overall survival in the transplant arms [23, 24]. The North American Intergroup trial has only been reported at meetings and results will soon be submitted for publication [25]. The results of this trial are difficult to interpret, but addition of total body irradiation, which actually impairs results of high-dose melphalan treatment and which nowadays has been abandoned from all conditioning regimens for autologous transplantation, may partly account for the modest improvement with the transplantation regimen. Overall, autologous transplantation yields median survival between 5 and 6 years. The long time to tumor progression results in a significant prolongation of the time without symptoms of disease and/or toxicity of treatment and, hence, improved quality of life.

The addition of a second autologous transplantation with melphalan 200 mg/m\(^2\) leads to further improvement of treatment outcome. This has been shown by the French IFM 94 trial comparing single with double transplantation. Double autologous transplantation yielded superior response rates, and progression-free and overall survival [23]. Patients who achieve complete or a very good partial response after first autotransplant do not seem to need a second autotransplant, since results did not differ between single and double transplantation in this good prognosis group. Patients with incomplete response to first transplantation, however, should be offered a second autologous transplantation since their survival has been shown to be significantly increased by the second transplant. Similar results have recently been shown in an Italian trial [27], but other studies with only short follow-up and different trial design have as yet not confirmed the impact of double transplantation.
Maintenance treatment

Depending on the initial type of treatment, tumor and patient characteristics, median duration of remission usually amounts to 12–18 months after conventional therapy and to ~30 months after high-dose chemotherapy. Eventually, almost all patients relapse. Studies aimed to identify treatments that enhance remission duration revealed that prednisone 50 mg on alternate days results in a significant prolongation of remission duration and of overall survival as compared with prednisone 10 mg on alternate days [28]. Interferon-α, 3 MU three times a week has been shown to increase remission duration and overall survival by 6 months [29, 30]. Interferon may induce side-effects, leading patients to discontinue treatment. One study showed that 80% and 60% of patients continued on interferon treatment after 1 year and after 2 years, respectively.

Table 2. Overall response rates in newly diagnosed patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Schedule</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan–prednisone [11]</td>
<td>M 0.25 mg/m² days 1–4 &lt;br&gt;P 50 mg/m² days 1–4, every 4–6 weeks</td>
<td>40–60</td>
</tr>
<tr>
<td>Dexamethasone [12]</td>
<td>D 40 mg, days 1–4, 9–12, 17–20 on uneven cycles, days 1–4, 17–20 every 4–5 weeks</td>
<td>40</td>
</tr>
<tr>
<td>VAD [13]</td>
<td>V 0.5 mg/m² days 1–4, cont. inf. &lt;br&gt;A 9.0 mg/m² days 1–4, cont. inf., q 4–6 weeks &lt;br&gt;D 40 mg, days 1–4, 9–12, 17–20 on uneven cycles, days 1–4, 17–20 on even cycles</td>
<td>50–70</td>
</tr>
<tr>
<td>VMCP [14]</td>
<td>V 1 mg/m², day &lt;br&gt;1 M 6 mg/m², days 1–4 orally C 100 mg/m², days 1–4 orally P 60 mg/m², days 1–4 orally</td>
<td>50–65</td>
</tr>
<tr>
<td>Thalidomide–dexamethasone [8]</td>
<td>T 50–400 mg/day &lt;br&gt;D 40 mg, days 1–4, 9–12, 17–20 on uneven cycles, days 1–4, 17–20 on even cycles</td>
<td>60</td>
</tr>
<tr>
<td>Thalidomide–dexamethasone chemotherapy [9]</td>
<td>As above plus either melphalan or doxorubicin or other chemotherapy</td>
<td>70–80</td>
</tr>
<tr>
<td>DCEP [15]</td>
<td>D 20–40 mg, days 1–4 &lt;br&gt;C 400 mg/m², days 1–4 cont. inf. &lt;br&gt;E 40 mg/m², days 1–4 cont. inf. &lt;br&gt;P 15 mg/m², days 1–4 cont. inf.</td>
<td>60–70</td>
</tr>
<tr>
<td>Bortezomib [16]</td>
<td>B 1.3 mg/m² days 1, 4, 8 and 11 every 21 days</td>
<td>35–45</td>
</tr>
<tr>
<td>Bortezomib–adriamycin–dexamethasone [17]</td>
<td>B 1.3 mg/m² days 1, 4, 8 and 11 every 21 days &lt;br&gt;A 9 mg/m² days 1–4 cont. inf., every 21 days &lt;br&gt;D 40 mg, days 1–4, 9–12, 17–20., every 21 days</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Lenalidomide [18]</td>
<td>L 10–25 mg/day</td>
<td>30–35</td>
</tr>
<tr>
<td>Autologous transplantation [19]</td>
<td>M 200 mg/m² plus autologous stem cells (≥2×10⁹/kg)</td>
<td>60–90</td>
</tr>
<tr>
<td>Non-myeloablative allogeneic transplantation [20]</td>
<td>2 Gy total body irradiation (or other conditioning regimens) plus allogeneic stem cells</td>
<td>60–85</td>
</tr>
</tbody>
</table>

V, vincristine; A, adriamycin; D, dexamethasone; T, thalidomide; M, melphalan; C, cyclophosphamide; P, prednisone; P, platinum; B, bortezomib; L, lenalidomide; E, etoposide.

Table 3. Results of high-dose therapy (HDT) with autologous transplantation versus combination therapy (CC)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Protocol</th>
<th>Patients (n)</th>
<th>Complete remission rate (%)</th>
<th>Progression-free survival (months)</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 90</td>
<td>HDT</td>
<td>200</td>
<td>38 incl. VGPR</td>
<td>28</td>
<td>57</td>
</tr>
<tr>
<td>Attal et al. [19]</td>
<td>CC</td>
<td></td>
<td>14 incl. VGPR</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>MRC VII</td>
<td>HDT</td>
<td>407</td>
<td>44</td>
<td>31</td>
<td>54</td>
</tr>
<tr>
<td>Child et al. [21]</td>
<td>CC</td>
<td>8</td>
<td>20</td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>Italian MMSG</td>
<td>HDT</td>
<td>401</td>
<td>44</td>
<td>32</td>
<td>58</td>
</tr>
<tr>
<td>Palumbo et al. [22]</td>
<td>CC</td>
<td>8</td>
<td>20</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>MAG 91</td>
<td>HDT</td>
<td>190</td>
<td>NA</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>Fermard et al. [24]</td>
<td>CC</td>
<td></td>
<td>NA</td>
<td>19</td>
<td>50</td>
</tr>
<tr>
<td>PETHHEMA</td>
<td>HDT</td>
<td>164</td>
<td>30</td>
<td>42</td>
<td>72</td>
</tr>
<tr>
<td>Blade et al. [25]</td>
<td>CC</td>
<td>11</td>
<td>33</td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>Intergroup</td>
<td>HDT</td>
<td>899</td>
<td>17</td>
<td>25</td>
<td>62</td>
</tr>
<tr>
<td>Crowley et al. [26]</td>
<td>CC</td>
<td>15</td>
<td>21</td>
<td></td>
<td>53</td>
</tr>
</tbody>
</table>

VGPR, very good partial remission; NA, not available.
New approaches investigate the impact of thalidomide maintenance treatment. Preliminary results indicate that thalidomide may lead to further improvement of response rates and maintenance duration [31], but is poorly tolerated by a large proportion of patients, making dose reductions or discontinuation of treatment mandatory in up to 80% of patients [32].

**Allogeneic transplantation**

Owing to remarkably long-standing remissions obtained in some individuals with multiple myeloma treated by allogeneic transplantation, it was hoped that further refinement of the technology might improve outcome. Unfortunately, all retrospective comparisons between allogeneic and autologous transplantation have been unable to show superiority of allogeneic transplantation [33]. The Intergroupe Francophone du Myelome is presently comparing tandem transplantation with autotransplantation followed by non-myeloablative allogeneic transplantation in patients with poor-risk myeloma (Del 13). Preliminary data indicate no benefit for allogeneic transplantation. Ongoing European Group for Bone Marrow Transplantation retrospective analysis shows inferior results with conventional allotransplantation in practically all patients cohorts compared with conventional treatments. Nevertheless, further refinements of the technology have been introduced. Non-myeloablative allotransplantation uses less intensive conditioning treatment and is offered to patients up to age 60 years. The 100-day transplant-related mortality is usually below 20% and in some centers even lower than 10%. The sequential treatment concept with initial autologous transplantation for reduction of tumor load and improvement of performance status followed by non-myeloablative allotransplantation is used in most centers [20]. Mortality is lower during the first months but late complications, in particular graft-versus-host disease, are more severe and frequent. Allogeneic transplantation, if successful, offers the hope for cure, which is not seen with autologous transplantation.

**Treatment of relapsing/refractory patients**

Patients who relapse after having been in remission for several months (>6 months) may be re-induced with the same regimen used for first-line therapy. In good-risk patients, single-agent dexamethasone therapy may even be considered. Responses are usually seen in 20–40% of cases. Patients relapsing early or with primary refractory disease need effective second-line therapy, which may be categorized as (i) purely cytostatic regimens, (ii) thalidomide-containing combinations, (iii) bortezomib and bortezomib combinations, and (iv) transplantation.

Traditional chemotherapy regimens such as VAD [13], VMCP [14] and DCEP [15] still have an important role, and induce responses in ~30–70% of patients.

Thalidomide-containing regimens include thalidomide in combination with dexamethasone (response rates 30–50%) and thalidomide–dexamethasone–cytostatic drug regimens (response rates 40–70%), which are more effective but also more toxic and make prophylaxis with low molecular weight heparin or aspirin mandatory [34].

Bortezomib has recently been introduced for treatment of patients with myeloma failing two or more treatment lines [10]. Bortezomib exhibits synergistic activity with dexamethasone and cytostatics. Importantly, it seems to revert resistance to cytostatic drugs. Single-agent bortezomib results in a 35% response rate in heavily pretreated patients.

Autologous transplantation is an effective therapy for relapsed patients. In fact, a study comparing first-line autologous transplantation with transplantation after relapse with conventional chemotherapy showed similar survival for both groups. Time to progression and quality of life, however, were superior in patients transplanted early [35]. Non-myeloablative allogeneic transplantation may be offered to selected patients.

**New treatments**

Bortezomib has significantly expanded the therapeutic armamentarium for patients with relapsing/refractory myeloma. Bortezomib induces remissions in one-third of heavily pretreated patients. The remission rate can be increased by combination with dexamethasone and further by additional combination with cytostatic drugs. Alternatively, a patient may be started on single-agent bortezomib therapy; in case of unresponsive-ness or relapse, dexamethasone may be added. This will render responses in additional 20% or re-induce remission. After subsequent relapse, a cytostatic drug may be added. This will result in renewed responses in a proportion of patients.

Preliminary data on first-line treatment with bortezomib and dexamethasone, bortezomib–dexamethasone–thalidomide and bortezomib–dexamethasone–doxorubicin regimens revealed responses in 83%, 84% and 93% of patients, respectively [17, 36, 37]. Importantly, time to response is short and usually ~4 weeks and tolerance is remarkably good. The most frequent side-effects of bortezomib are thrombopenia, neutropenia, diarrhea and sensory neuropathy. Most of these are of grade 1–2. Dose reductions or discontinuation of treatment is only rarely required (<10%), and mostly due to neuropathy and thrombopenia.

Lenalidomide (Revlimid®), a derivative of thalidomide, is active in relapsing/refractory patients, showing responses in ~35% of patients. A lenalidomide–dexamethasone combination proved effective in 41% [38] and vincristine–doxyl–dexametha- sone–lenalidomide produced responses in 70% of heavily pretreated patients [39]. In newly diagnosed patients, lenalidomide–dexamethasone induced remissions in 83% of patients [18].

Arsenic trioxide in combination with ascorbic acid, dexamethasone or melphalan is currently being studied in patients with advanced disease [40].

Several other promising drugs are presently being tested. Among those, vascular endothelial growth factor inhibitors [bevacizumab (Avastin®), inhibitors of histone deacetylase (SAHA), farnesyl transferase, RANKL and monoclonal antibodies look the most promising.
Acknowledgements

Supported by the Wilhelminen Cancer Research Institute of the Austrian Forum Against Cancer.

References


39. Hussein MA, Ann Karam MA, Brand K et al. Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and Revlimid® (DVd-R) a phase I/II trial in advanced relapsed/refractory multiple myeloma (Rmm) patients. Blood 2004; 104: (Abstr 208).