educational session

Hematological malignancies

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Hematological malignancies: myeloma

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introduction

Multiple myeloma (MM) is a plasma cell neoplasia, which accounts for more than 10% of all hematological malignancies. Most patients present with symptoms, signs and laboratory abnormalities suggestive of active disease, including painful osteolytic lesions, hypercalcemia, anaemia and renal impairment.

In recent years, an increasing number of patients are being diagnosed with MM by chance through screening for other reasons [1]. In a significantly larger number of individuals, an isolated finding of a monoclonal protein in the serum may lead to the diagnosis of monoclonal protein of undetermined significance (MGUS). The latter two conditions should be recognized and diagnosed correctly because they require no treatment. Such individuals require a lifelong observation in order to detect promptly patients at risk for complications and initiate the appropriate treatment. New diagnostic criteria have been recently established that allow a more homogenous classification of these disorders (Table 1) [2].

Several prognostic factors have been used over the years in order to stratify patients with MM in prognostic subgroups. Some of the most widely used variables include age, β2-microglobulin, albumin, lactate dehydrogenase, C-reactive protein, platelet count, abnormal karyotype, and plasma cell microglobulin, albumin, lactate dehydrogenase, c-reactive protein, (and their oncogenes) translocations (referred as primary IgH translocations) that are positioned near a strong Ig enhancer sequence [6]. Translocations that involve both the IgH and light-chain (IgL) genes have been implicated as seminal events in the pathogenesis of MM [7].

The prevalence of these IgH (chromosome locus 14q32) translocations is somewhat correlated with the disease stage: 50% of MGUS or asymptomatic multiple myeloma (AMM), 55–73% of intramedullary MM, 85% of plasma cell leukemia (PCL) and >90% of human myeloma cell lines (HMCL) are characterized by these translocations [8, 9].

About 40% of MM have five recurrent chromosomal partners (and their oncogenes) translocations (referred as primary IgH translocations) evolved through the IgH translocation process: 4p16 (MMSET and usually FGFR3) (15%), 6q21 (CCN D3) (3%), 11q13 (CCN D1) (15%), 16q23 (c-MAF) (5%) and 20q11 (MAFB) (2%) [10]. There is less information about IgL translocations, occurring in about 10% of MGUS/AMM tumors and 20% of advanced intramedullary MM tumors and HMCLs, while translocations involving the IgL-k locus are quite rare [11]. Another 20–30% of MM cases have translocations that involve chromosome partners that occur at a prevalence of 1% or less and are referred as secondary translocations [12]. Secondary translocations are not mediated through the B-cell specific DNA modification mechanisms and, in contrast to primary translocations described earlier, involve partners like c-myc (8q24), a late event in the pathogenesis of PC tumors, often include unbalanced and complex translocations and insertions that can involve three chromosomes, sometimes with associated amplification, duplication, inversion, or deletion. IgL translocations are considered early genetic lesions because their prevalence in MGUS is nearly as high as in MM although the prevalence of specific partners may be different for MGUS and MM [11].

Another feature of all MGUS and MM tumors is the presence of numeric and/or structural chromosome abnormalities [9, 13]. Using interphase fluorescence in situ hybridization (FISH), we now know that chromosomal abnormalities are nearly universal and are early events in the PC neoplasms. Two major ploidy categories have been proposed [9, 14] in MM: the hyperdiploid myeloma (HRD), which is characterized by the increased prevalence of multiple trisomies involving eight odd chromosomes (chromosomes 3, 5, 7, 9, 11, 15, 19, 21) and the non-hyperdiploid (NHRD) tumors which can be hypodiploid, pseudodiploid or subtetraploid and are associated with increased prevalence of primary IgH translocations [15]. It is not clear whether translocations or aneuploidy occur first but NHRD tumors were noted to have a poorer prognosis.

pathogenesis

MM is a tumor of somatically mutated plasma cells (PCs) that accumulate in the bone marrow (BM) leading to bone destruction and BM failure. PCs evolve from post germinal center B-cells through processes that include modification of their immunoglobulin (Ig) genes by sequential rounds of somatic hypermutation, antigen selection and Immunoglobulin-Heavy-Chain (IgH) switch recombination. These DNA modifications sometimes may cause mutations or breaks in the double-stranded DNA in locations in or near of non-Immunoglobulin genes, including oncogenes. The consequence of these modifications is the increased expression of oncogenes (mostly proliferation genes and transcriptional factors) that are positioned near a strong Ig enhancer sequence [2].

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than HRD tumors. Chromosome 13 deletions or monosomy, a well recognized adverse prognostic factor, is also much more common in NHRD tumors (72% versus 37% in HRD) but it remains to be clarified whether ploidy or loss of chromosome 13 are independent prognostic factors [16].

Recent analyses from gene expression profiling suggest that in virtually all MM and MGUS tumors, including those with or without a IgH translocation, at least one of the cyclin D genes (D1, D2 or D3) is expressed at a high level compared with normal PCs [17]. About 25% of MGUS or MM tumors have IgH translocations that directly dysregulate cyclin D1 (11q13, CCN D1), cyclin D3 (6p21, CCN D3) or dysregulate transcription factors that target cyclin D2 (16q23, MAF and 20q11, MAFB). Nearly 40% of MGUS and MM do not have a t(11;14) but are HRD and bi-allelically express cyclin D1 while most other tumors including those with a t(4;14) also have increased expression of Cyclin D2 [17].

Based on the available data it has been proposed [9, 13, 17] that there are two distinct pathways in the pathogenesis of MM: one involving an early IgH translocation that usually includes one of the five recurrent partners and mostly is associated with non-hyperdiploid chromosome content and a second, that infrequently, if ever, involves early IgH translocation and is associated with hyperdiploid chromosome content and multiple trisomies, perhaps as a reflection of intrinsic genetic instability, through yet unetermined mechanisms. Dysregulation of a cyclin D gene appears to be a unifying and early event in the pathogenesis of MM [17] although does not seem sufficient to lead to tumor development unless there is a cooperating activation of other oncogenes like myc or ras or inactivation of genes like p16INK4a, p11NK4b. Nevertheless cyclin D overexpression may render the cells more susceptible to proliferative signals produced by interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1) and other cytokines as a result of their interaction with bone marrow stem cells (BMSCs) [13].

Based on the hypotheses presented above gene expression profile (GEP) studies provided the basis for a molecular classification of MM [14, 17] into eight groups distinguished by the Ig translocation present and Cyclin D expression. In addition to shared gene expression profiles, important biologic and clinical correlates have been identified. Plasma cell leukemia and myeloma cell lines are absent from the D1 group (hyperdiploid tumors with high levels of cyclin D1 and low proliferative index) while MGUS cases fall neatly into 5 certain groups. Lytic bone lesions have high prevalence (>90%) in certain groups and lower in others (55–57%). Groups characterized by certain translocations, like t(4;14) (group 4p16) or t(14;16) (group maf) have a substantially shortened survival (26 and 16 months with conventional therapy respectively) while other (group 11q13) appears to have a better survival following both conventional chemotherapy and high-dose therapy. This molecular classification model needs to be further validated and perhaps modified in the future as our knowledge in the biology of MM increases and our therapeutic armentarium expands.

### standard chemotherapy

Oral melphalan and prednisone (MP) was first introduced in 1968 and was established as the first effective combination for the initial treatment of patients with symptomatic MM. The objective response rate is approximately 50%; complete responses are rare and median survival is less than 3 years [1]. Because of the limitations of MP, several combinations of multiple alkylating agents administered with or without the addition of a vinca alkaloid, an anthracycline or a nitrosourea have been used. Despite initial enthusiasm for such combinations, an overview by the Myeloma Trialist’s Collaborative Group, showed that MP and combination therapy were comparable in effectiveness [18].

A significant step forward was the description of the VAD regimen, which combines vincristine and doxorubicin, administered by continuous intravenous infusion for 4 days with high dose oral dexamethasone pulses. This regimen, which was active in many patients that were resistant to alkylating agents, has been administered to previously untreated patients. The response rate was approximately 60% but it offered no obvious survival benefit compared with standard alkylating agent-based therapies. However, the time to reduce the
monoclonal protein by half was less with VAD than with other regimens that did not include high-dose steroids [19]. Because VAD is a stem cell-sparing regimen it has been considered as the gold standard induction treatment for patients with MM who were eligible for stem cell collection to support high-dose therapy. High-dose intermittent oral dexamethasone also proved to be an active primary therapy, with response and survival rates similar to those achieved with alkylating agent-based combination or with VAD [20].

**High-dose therapy**

Based on pioneering work performed by McElwain and by Barlogie two decades ago, several studies have evaluated the role of high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) in the management of patients with MM [21, 22].

**Single autologous transplant**

Use of high-dose melphalan with ASCT is a major advance in the therapy of MM. To date five randomized studies have compared the outcome of patients treated with HDT versus standard dose therapy (SDT) (Table 3). The Intergroup Français du Myelome 90 (IFM 90) and the Medical Research Council (MRC) II trials showed significantly increased complete response (CR) rates, with prolonged event-free survival (EFS) and overall survival (OS) in the patient cohorts receiving HDT [23, 24]. In contrast, the Myelome-Autogreffe Group (MAG) which included patients aged 55 to 65 years showed a benefit of HDT in terms of EFS and time without symptoms, treatment and treatment toxicity (TwiSTT) but without OS benefit [25]. These three trials indicated a transplant-related mortality of 1% and a transplantation exclusion rate of 25%. The US Intergroup trial, which randomized patients to HDT versus SDT with delayed HDT at relapse, did not show superiority of HDT for either achievement of CR or prolongation of OS [26]. Finally, the Spanish Cooperative group PETHEMA compared HDT intensification versus continued standard chemotherapy in patients responding to the initial chemotherapy. This study showed significantly higher CR rates after HDT without statistically significant improvement EFS and OS [27].

A critical analysis of the above listed trials may indicate that a clear benefit of HDT is observed only in those randomized studies with significantly lower CR rates after SDT, supporting the view that achieving higher CR rates is associated with prolonged survival. Furthermore, HDT may mainly benefit patients with disease refractory to SDT as suggested by the absence of any survival difference between the two strategies when administered as a consolidation treatment in responders to an initial SDT. Finally, despite an extended EFS in some patients, HDT is not considered as a curative approach in patients with MM.

**Tandem autologous transplant**

One approach to improve the outcome after HDT is to administer to patients a second HDT with ASCT after they have recovered from the first. This tandem transplantation approach was developed by Barlogie and colleagues in an attempt, to improve complete response rates [4]. So far, five randomized trials evaluated the role of tandem HDT in the management of patients with MM (Table 3) [28–32]. In two of these studies there is evidence of improved EFS after tandem transplantation and in the IFM trial there was a survival advantage for patients who had achieved less than a very good partial response (PR) after the first transplantation [28].

Based on the above data, it is reasonable to consider tandem transplantation for patients who do not have at least a very good partial response (i.e. ≥90% reduction in monoclonal protein levels) with the first HDT. Alternatively, it may be prudent to collect enough stem cells after induction therapy to allow a patient to undergo two HDT, one early in the course of the disease and the other HDT at the time of relapse.

**Novel agents for relapsed/refractory myeloma**

After SDT or HDT, essentially all myeloma patients ultimately relapse with tumor that is refractory to further treatment. Recent advances in molecular genetics provided the opportunity to identify tumor-specific pathways that regulate myeloma cell growth and survival. Furthermore, the combination of the tumor microenvironment to the growth and survival of myeloma cells has identified myeloma cell interactions with the microenvironment as a potential therapeutic target. Herein, we will provide data on the role of three clinically available agents that have been through the process of phase II or phase III trials i.e. thalidomide, bortezomib and lenalidomide.

**Thalidomide**

Multiple studies, which have included thousands of patients with relapsed/refractory myeloma, have shown that thalidomide can induce a PR in approximately 30% [33–35]. The responses are durable, with a median duration of approximately 12 months. The median time to response after thalidomide ranges from 4 to 8 weeks, while the probability for 1- and 2-year OS is 58% and 48% respectively (Table 4). Thalidomide may have

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**Table 3.** Randomized trials of high-dose treatment with autologous stem cell support in myeloma

<table>
<thead>
<tr>
<th>Author [Reference]</th>
<th>%CR</th>
<th>EFS months</th>
<th>OS months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single HDT versus SDT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attal (1996) [23]</td>
<td>22 versus 5*</td>
<td>28 versus 18*</td>
<td>57 versus 42*</td>
</tr>
<tr>
<td>Child (2003) [24]</td>
<td>44 versus 9*</td>
<td>32 versus 20*</td>
<td>55 versus 42*</td>
</tr>
<tr>
<td>Blade (2003) [27]</td>
<td>30 versus 11*</td>
<td>42 versus 33</td>
<td>61 versus 66</td>
</tr>
<tr>
<td>Tandem HDT versus Single HDT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attal (2003) [26]</td>
<td>50 versus 42</td>
<td>30 versus 25*</td>
<td>58 versus 48*</td>
</tr>
<tr>
<td>Cavo (2005) [29]</td>
<td>–</td>
<td>–</td>
<td>73 versus 59</td>
</tr>
<tr>
<td>Sonneveld (2005) [31]</td>
<td>28 versus 13*</td>
<td>22 versus 20</td>
<td>50 versus 55</td>
</tr>
</tbody>
</table>

*P ≤ 0.05; CR, complete response; EFS, event-free survival; OS, overall survival; HDT, high-dose therapy; SDT, standard dose therapy.
multiple mechanisms of action against myeloma including the inhibition of tumor necrosis factor alpha, the suppression of angiogenesis, the altered expression of cellular adhesion molecules and a direct anti-myeloma effect [36].

Subsequent trials explored its use in combination with other active agents in the treatment or relapsed/refractory myeloma. Several reports have indicated that the combination of thalidomide with dexamethasone is active in 50% of patients with advanced myeloma and that the median time to response is one month or less [35, 37]. Thalidomide and dexamethasone have been combined with several chemotherapeutic agents, the most common being cyclophosphamide [35, 38]. Table 4 suggests that thalidomide and dexamethasone is more effective than single agent thalidomide since the 95% confidence intervals for the response do not overlap. Whether a combination of thalidomide, dexamethasone and cyclophosphamide may be more effective than thalidomide and dexamethasone is less clear [35].

Administration of thalidomide is associated with several side effects including somnolence, constipation, fatigue, xerostomia and edema. A significant side effect of thalidomide is deep venous thrombosis (DVT). The frequency of this complication is 5% or less when thalidomide is used alone, but increases to near 15% when thalidomide is given with dexamethasone. Thus prophylactic anticoagulation, preferably with low molecular weight heparin, is required. Another important adverse effect is peripheral neuropathy which is dose-and time-dependent and is the major cause of dose reduction or discontinuation of thalidomide [39].

### Bortezomib

Bortezomib is a small molecule that is a potent and reversible inhibitor of the proteasome, which is the primary component of the protein degradation pathway of the cell. Bortezomib inhibits proliferation and induces apoptosis of human myeloma cells in vitro. It also inhibits nuclear factor-kappa B (NF-KB) activation, overcomes drug resistance and adds to the anti-myeloma-activity of dexamethasone, melphalan and doxorubicin in vitro.

In the large APEX trial, bortezomib was shown to be more effective than dexamethasone as far as response, time to progression and OS are concerned (Table 4) [40]. A recent update of the APEX trial showed an improved response rate, which reached 43% with extended use of bortezomib. The median duration of response is 11.5 months for patients who reached CR or near CR and 7.6 months for patients rated as PR [41].

Bortezomib has been approved as second- or third-line treatment of patients with MM. The most common side effects of bortezomib include diarrhea, fatigue, fever, cytopenia and peripheral neuropathy. Short-lived thrombocytopenia occurs in 30% of patients. Peripheral neuropathy, which can be painful, occurs in 30% of patients. This complication is reversible with appropriate dose reduction or discontinuation of treatment. Other less common complications consist of orthostatic hypotension and hyponatremia [40].

The combination of bortezomib, thalidomide and dexamethasone has shown activity in 55% of patients most of whom have been previously treated with thalidomide [42] (Table 4). Bortezomib has also been administered in combination with melphalan, doxorubicin or cyclophosphamide with encouraging results.

### Lenalidomide

The design and synthesis of thalidomide analogues is an ongoing research effort to obtain compounds with enhanced activity and favorable toxicity profile. Among them,

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Response rate (CI)</th>
<th>EFS</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>200–400 mg PO daily</td>
<td>29 (27–32)</td>
<td>10 mo</td>
<td>19 mo</td>
<td>Barlogie 2001 [34]</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>100–200 mg PO daily</td>
<td>55</td>
<td></td>
<td></td>
<td>Dimopoulos 2001 [37]</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>40 mg PO for 2 or 3 four-day pulses every 28 days</td>
<td>51 (45–57)</td>
<td></td>
<td></td>
<td>Glasmacher 2005 [35]</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>as above</td>
<td>57 (45–67)</td>
<td></td>
<td></td>
<td>Garcia-Sanz 2004 [38]</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>50 mg PO daily</td>
<td>60 (55–65)</td>
<td></td>
<td></td>
<td>Glasmacher 2005 [35]</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² IV on days 1, 4, 8, 11 every 21 days</td>
<td>38</td>
<td>6.2 mo</td>
<td>80% at 1 year</td>
<td>APEX [2005] [40]</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>100–200 mg PO daily</td>
<td>55</td>
<td>9 mo</td>
<td>22 mo</td>
<td>Zangari 2005 [42]</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg PO days 1–4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² IV on days 1, 4, 8, 11 every 21 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg PO daily for 21 days every 28 days</td>
<td>25</td>
<td>6 mo</td>
<td></td>
<td>Richardson 2005 [43]</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25 mg PO daily for 3 or four-day pulses every 28 days</td>
<td>59</td>
<td>11.3 mo</td>
<td>85% at 1 year</td>
<td>Dimopoulos 2005 [44]</td>
</tr>
</tbody>
</table>

EFS, event-free survival; OS, overall survival; CI, confidence interval; mo, months.
lenalidomide has been tested more extensively in patients with relapsed or refractory MM. The maximum tolerated dose is 25 mg/day orally (PO) for 21 days with a 7-day rest period.

The major toxicity is neutropenia and less common thrombocytopenia. Lenalidomide is not associated with significant constipation, somnolence and peripheral neuropathy. DVT can occur in up to 10% of patients but this complication can be prevented with the administration of low dose aspirin (81 to 325 mg PO daily).

A recent update of a large phase II study of lenalidomide which included 222 patients with relapsed/refractory MM showed a PR in 27% of patients [43]. Two large phase III studies, conducted in parallel, which compared lenalidomide plus dexamethasone with placebo plus dexamethasone have been reported recently (Table 4). Both trials indicated that the combination of lenalidomide with dexamethasone was associated with a three-times higher response rate five-times longer median time to progression. Furthermore, there is emerging evidence of a survival advantage for patients treated with lenalidomide and dexamethasone [44].

**current treatment approach of newly diagnosed symptomatic patients**

The development of novel agents with significant activity in relapsed/refractory myeloma resulted in phase II and phase III trials for previously untreated patients. These trials evaluated regimens suitable for patients who were candidates for HDT. The aim of these studies was to develop new non-stem cell toxic combinations, with improved response rate and with rapid anti-myeloma effect. Such combinations may decrease the percentage of patients who experience early disease progression and may improve the rate of proceeding to HDT. Furthermore, specific regimens are also being evaluated for elderly or unfit patients who are not considered candidates for HDT.

**primary treatment for patients eligible for HDT**

Phase II studies indicated that the combination of thalidomide and dexamethasone (TD) induced responses in approximately 70% of patients with previously untreated myeloma. With this oral regimen, responses occurred within one month, without evidence of myelosuppression [1]. A prospective randomized trial compared TD to single agent dexamethasone and confirmed higher response rates for the combination (63% versus 41%), low incidence of neuropathy and collection of adequate stem cell number to support HDT [45]. Furthermore, a retrospective comparison of TD with VAD showed improved response with TD, less myelosuppression and adequate stem cell collection [46]. These studies indicate that VAD should no more be considered as the standard induction regimen for patients who are eligible for HDT. Furthermore, bortezomib and dexamethasone has shown a high response rate and has provided the opportunity to collect sufficient numbers of stem cells [47]. Another phase II trial showed that lenalidomide and dexamethasone is also very effective (Table 5) [48]. Thus, combination of each of 3 novel agents with dexamethasone may be considered as an appropriate induction regimen before HDT. However, there is more experience with TD.

**primary therapy for patients not eligible for HDT**

The outcome of older patients treated with conventional chemotherapy is poor and has not improved over the last decades. Thus, there is a great need for more effective induction treatments in this group, which comprises the majority of patients with symptomatic myeloma.

Two prospective randomized trials have compared MP with MP plus thalidomide (MPT). Both trials showed that MPT was associated with higher overall response rate, higher CR rate, and longer EFS (Table 5) [49, 50]. One trial also showed a survival advantage for MPT when compared not only with MP but also with intermediate dose intravenous melphalan [50]. Preliminary results indicate that the addition of bortezomib to

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**Table 5.** New treatment for previously untreated myeloma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Response rate</th>
<th>EFS</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>200 mg PO daily</td>
<td>63</td>
<td>NA</td>
<td>NA</td>
<td>Rajkumar 2006 [45]</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg PO for 3 four-day pulses every 28 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td>9 mg/m² days 1–4</td>
<td>81</td>
<td>30 mo</td>
<td>55 mo</td>
<td>Facon 2005 [50]</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m² days 1–4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>100 mg PO daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² IV</td>
<td>89</td>
<td>NA</td>
<td>NA</td>
<td>Jagannath 2005 [47]</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg PO PO days 1, 4, 8, 11</td>
<td>86</td>
<td>NA</td>
<td>NA</td>
<td>Mateos 2005 [51]</td>
</tr>
<tr>
<td>Melphalan</td>
<td>9 mg/m² days 1–4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m² days 1–4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² IV on days 1, 4, 8, 11, 22, 25, 29, 32 every 6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg PO daily for 21 days</td>
<td>91</td>
<td>NA</td>
<td>NA</td>
<td>Rajkumar 2005 [48]</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg PO for 3 four-day pulses every 28 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EFS, event-free survival; OS, overall survival; mo, months.
MP is associated with a 90% response rate [51] (Table 5). Thus, it is reasonable to suggest, that MP should not be considered the standard primary treatment for patients not eligible for HDT. Based on data from randomized studies, MP T appears now to represent the new standard of care. However, this regimen has been tested, in the context of randomized trials in patients younger than 75 years of age. There is no information regarding the efficacy and safety of MP in older patients.

future directions

Apart thalidomide, bortezomib and lenalidomide, novel biological therapies, which target both tumor cell and its microenvironment are under development. Many of these agents have multiple biologic activities. Combinations of new treatments with older drugs may enhance cytotoxicity, and avoid drug resistance. Finally, gene microarray and proteomics may help define in vivo targets that confer resistance and provide the framework for development of more selective, potent and less toxic therapies.

references

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