[haematologica reports]
2006;2(7):36-39

Are there differences in the treatment strategies and outcomes between high-risk multiple myeloma patients and those with low-risk disease and without comorbities?

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It is well recognized that multiple myeloma (MM) is a B-cell malignancy with great variability in clinical outcome: Median survival times are approximately 3 years with standard-dose therapy and about 4 to 5 years with intensive treatment programs, but survival may range between only a few months and more than 10 years. Therefore, it has been a relevant issue to identify prognostic indicators for the estimation of the individual patient's outcome. Development of strategies to optimize treatment, particularly with the aim of risk-adapted therapies, has gained substantial importance due to the availability of *novel* agents for MM therapy.

Standard clinical and laboratory parameters as prognostic parameters in MM

In 1975, Durie and Salmon proposed a staging system based upon readily available clinical parameters (serum hemoglobin, size of the paraprotein, serum calcium, and number of osteolytic bone lesions by skeletal radiography).[1] The Durie and Salmon staging system, which correlated with tumor burden and survival, was widely used despite its limitations, in particular with respect to the definition of bone lesions. Therefore, the search for more accurate prognostic factors continued, and several studies identified demographics, features of the tumor itself, and laboratory abnormalities as prognostic indicators for survival (compare Table 1).[2-5]

More recently, an international cooperative project aimed at the identification of a simple and reliable staging system for MM was initiated. Clinical and laboratory parameters from 10750 previously untreated, symptomatic patients with MM were collected (69.1% from clinical trial data). The most powerful classification system was obtained by a combination of serum β_2-microglobulin (β_2-M) and serum albumin (Table 2).[10] This International Staging System (ISS) was validated in various MM patient populations: It was found to be effective in MM patients independent of age (less or more than 65 years of age), type of therapy (standard dose or autologous transplantation) and geographic region (North America, Europe, and Asia). By now, it is suggested to use the ISS staging system, particularly in the setting of clinical trials. An improved definition of patients at risk is expected in the future by incorporation of genetic and proteomic data.

Genetics and prognosis in MM

IgH-translocations

One of the most frequent structural abnormalities observed in MM karyotypes involves the Ig heavy-chain (IgH) gene locus on 14q32, which is usually part of a translocation. Heterogeneous translocation partners have been described, with 11q13, 4p16.3, 16q23, 20q11 and 6p21 being recurrently involved in 14q32 translocations of primary MM tumor specimens.[11] These 5 types of primary IgH-translocations, which are mutually exclusive, comprise about 60% of all IgH-translocations, and are mediated primarily by errors during IgH switch recombination. With respect to biology and prognosis, relevant correlations have emerged: the t(11;14)(q13;q32) resulting in upregulation of cyclin-D1 was origianally thought to characterize a favorable group of patients, in particular when treated with intensive therapy.[14] However, most recent results suggest that a t(11;14) does not affect event-free and overall survival,15-17 whereas presence of a t(4;14)(p16;q32) or a t(14;16)(q32;q23) identifies a subset of MM patients with short survival, even in the context of autologous transplantation.[14-18] Translocations t(4;14) and t(14;16) are also highly correlated with a deletion of chromosome 13q.

Additional chromosomal aberrations

By metaphase cytogenetics, a chromosome 13q abnormality can be found in about 15% of MM patients at diagnosis, whereas interphase FISH studies have shown a higher frequency of 13q deletions

Table 1. Summary of prognostic factors.

Demographic factors	Advanced age (> 70 years)[2] Standard-dose chemotherapy > 12 months[3]
Features of the tumor clone	IgA isotype[3,4] Increased proliferative activity (high labeling index, high S-phase)[1,5,6] Chromosomal abnormalities (translocation t(4;14), deletion 17p, deletion 13q) [13-23] High microvessel density7
Laboratory abnormalities	Anemia (hemoglobin < 10 g/dL)[2] Elevated creatinine[2] High serum LDH[8] High serum CRP[9] Low serum albumin[10] High serum β-2-microglobulin[2-5,10]

Table 2. International Staging System (ISS) for multiple myeloma.[10]

Stage	*% of patients*	*Features*	*Median survival*
I	28	β-2-microglobulin <3.5 mg/L albumin ≥3.5 g/dL	62 months
II	33	β-2-microglobulin <3.5 mg/L albumin < 3.5 g/dL or β-2-microglobulin 3.5 – 5.5 mg/L	44 months
III	39	β-2-microglobulin ≥5.5 mg/L	29 months

in MM, occurring in 39–54% of newly diagnosed cases. Several studies have reported a strong association of a deletion 13q with an unfavorable prognosis of MM patients (summarized in [19]). It appears that chromosome 13 abnormalities are a more powerful predictor of poor outcome when identified by karyotyping.[20] The negative prognostic impact of a deletion 13q seems to persist even in the context of allogeneic stem cell transplantation.[21]

Clinical importance was reported for deletions of 17p13 at the *TP53* locus, with similar observations for patients receiving standard-dose and high-dose therapy.[15–17,22] Comprehensive analyses of cytogenetic abnormalities in MM identified patients with a t(4;14) and/or 17p-deletion as the group of patients with the worst prognosis suggesting that novel approaches are required for the treatment of such high-risk patients.

Studies done by the Arkansas group identified a region on chromosome 1, which was linked with an aggressive clinical course in MM: Global gene expression profiling on plasma cells from newly diagnosed patients treated with autologous transplantation revealed a significant over-representation of chromosome 1 genes in a group of about 70 genes whose expression was associated with poor outcome. Further analyses showed that overexpression of CKS1B was strongly correlated with a gain of DNA copy numbers at chromosomal region 1q21, and that this abnormality conferred a poor prognosis.[23] As a possible mechanism, reduced levels of $p27^{Kip1}$ protein were observed in cases with 1q21 amplification, suggesting dysregulated cell cycle control in these cases.

Gene expression profiling in MM

Today, genome-wide gene expression profiling based on DNA microarrays represents one of the most powerful tools in the area of genomics. This technique has become feasible and broadly accessible, and in MM it is a valuable tool to identify all myeloma-specific genetic abnormalities on a single platform.[24] When this technique was used to identify genes associated with therapeutic outcome in 221 patients with previously untreated MM, unsupervised clustering led to the identification of four distinct MM subgroups.[24] Further studies indicated that three genes of this analysis can be used to predict event-free survival. Furthermore, gene expression profiling provided the basis for a novel molecular classification of MM because overexpres-

Table 3. TC molecular classification of MM as proposed by Bergsagel and Kuehl.[25]

Group	*Translocation*	*Gen(s)*	*CyclinD*	*Ploidy*[a]	*%*
TC1	t(11;14)(q13;q32)	cyclinD1	D1	NH	15
	t(6;14)/p21;q32)	cyclinD3	D3	NH	3
TC2	None	None	D1	H	37
TC3	None	None	D2	H = NH	22
TC4	t(4;14)(p16;q32)	fgfr3/mmset	D2	NH > H	16
TC5	t(14;16)(q32;q23)	c-maf	D2	NH	5
	t(14;20)(q32;q11)	mafB	D2	NH	2

[a] *NH, non-hyperdiploid; H, hyperdiploid.*

sion of one of the cyclin-D genes was found to be universal molecular feature of MM.[25] The so-called TC-classification combines the cytogenetic information about the 14q-translocations with cyclin-D gene expression as summarized in Table 3. Patients of the TC4 and TC5 categories have shortened survival suggesting that they should be considered for clinical studies exploring investigational therapies.

Impact of novel agents on prognosis

By now, prognostic factors conferring a poor outcome in MM were defined according to the experience with chemotherapy, with no apparent differences between standard-dose and high-dose therapy (compare all studies referenced above). Recent studies have addressed the question whether or not treatment for high-risk patients may be improved by use of novel agents.

Thalidomide

Prognostic information is available mainly in patient populations treated with thalidomide in the relapsed/refractory setting. Among 75 patients treated with single agent thalidomide, advanced age (≥65 years), elevated serum LDH, and elevated serum creatinine were predictive for inferior outcomes.[26] In a similar analysis of relapsed MM patients treated with thalidomide-based regimens, elevated serum LDH, advanced ISS-stage, and reduced performance status were independent predictive factors for survival.27 Based on these three variables, a scoring system was developed with survival times of 38.1, 28.8, and 5.8 months for scores 0, 1, and 2, respectively. The authors concluded that the addition of LDH and performance status to the prognostic information provided by the ISS may help select patients who will likely derive benefit from treatment with thalidomide-based regimens.

According to the experience of the Arkansas-Group (phase 2 trial of single agent thalidomide in 169 patients with pretreated MM), favorable survival rates were observed in patients with normal metaphase cytogenetics, low proliferative activity (plasma cell labeling index < 0.5%) and serum β_2-M below 3 mg/L.[28] Overall, these results suggested that prognostic factors for treatment with thalidomide are similar to those observed with chemotherapy.

Bortezomib

In patients enrolled into the SUMMIT-trial, potential association between baseline-characteristics and outcome were explored.[29] By multivariate analysis, two parameters emerged as being significantly associated with lower response: age > 65 years and plasma cell infiltration > 50%. Parameters predicting for shortened overall survival were low serum albumin, bone marrow plasma cell infiltration > 50%, and thrombocytopenia. Of particular note, elevated serum β_2-M and presence of a chromosome 13q deletion (tested in a subset of study patients) were not predictive of poor outcome with bortezomib in this clinical trial.

Among patients treated in the APEX trial, a matched-pair analysis was performed between 21 patients with a deletion 13q (metaphase analysis) and 41 patients without this deletion.[30] Patients were balanced for other adverse prognostic factors including age, lines of prior therapy, β_2-M, and albumin. Presence of a chromosome 13q-deletion was associated with a markedly decreased survival in the dexamethasone-arm; in contrast, in the bortezomib arm, deletion 13q was not associated with a difference in survival or response rate.

In our own analysis of 51 patients with relapsed/refractory MM, treatment with single agent bortezomib resulted in similar response rates and duration of response in patients with and without a chromosome 13q-deletion.[31] Serum β_2-M did not emerge as a relevant parameter associated with treatment outcome after bortezomib (lack of prognostic information for response rate, time to treatment failure, and overall survival). Low serum albumin correlated with short time to treatment failure and poor overall survival, and low albumin identified also those patients with a deletion 13q who did not benefit from treatment with bortezomib.

Thus, although additional data from prospective clinical trials are needed, existing data indicate that prognostic factors established from chemotherapy trials cannot be uniformly applied to patient populations treated with bortezomib.

Conclusions and future directions

In conclusion, bortezomib has emerged as the only substance with remarkable activity in MM patients with adverse cytogenetic features. Our analysis also shows that favorable survival times are generally limited to those patients without additional adverse prognostic factors such as low serum albumin or amplification of chromosome 1q21. Future studies should explore the value of earlier initiation of bortezomib and of bortezomib combinations in patients with cytogenetic risk factors. Furthermore, studies should be continued to further evaluate the role of gene expression profiling for identification of high-risk patients likely to benefit from bortezomib and other novel drugs in MM therapy.

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