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Predictors of inferior clinical outcome in patients with standard-risk multiple myeloma

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Abstract

Introduction: Outcome of patients with standard-risk (SR) multiple myeloma (MM) has improved; however, subsets of patients do worse than expected. We sought to identify the factors associated with inferior outcome.

Methods: We evaluated 51 patients with SR MM that received upfront autologous hematopoietic stem cell transplantation (auto-HCT) after induction and had a progression-free survival (PFS) of ≤18 months.

Results: The median age of patients was 61 yr. Forty-one (80%) patients received induction with immunomodulatory drugs, proteosome inhibitors, or combination of both. The overall response rate (ORR) after auto-HCT was 96% (stringent complete response 23%, complete response 10%, very good partial response 22%, and partial response 39%). The median PFS was 7.8, and median overall survival (OS) was 56.3 months. On univariate analysis, concurrent light-chain amyloidosis (AL) was associated with inferior PFS [hematological response (HR); 2.51, 95% CI; 0.64–10.58, $P = 0.03$] and occurrence of soft tissue plasmacytoma was associated with a significantly shorter OS (HR: 3.05, 95% CI: 0.57–16.29, $P = 0.02$).

Conclusion: Our analysis suggests that concurrent AL and soft tissue plasmacytoma were associated with shorter PFS and OS, respectively. Heterogeneity in clinical outcome of SR MM merits better tools for prognostication, such as gene expression profiling and minimal residual disease assessment to identify high-risk patients.

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Conflict of interest

None.

Keywords

standard-risk multiple myeloma; autologous hematopoietic stem cell transplant; plasmacytoma; amyloidosis

Multiple myeloma is a heterogeneous disease with variable survival outcomes. Despite treatment with proteasome inhibitors (PI), immunomodulatory drugs (IMiDs), and autologous hematopoietic stem cell transplantation (auto-HCT) (1–5), overall survival (OS) remains highly variable, ranging from <2 yr to a decade or longer (1). Numerous studies have identified factors that may predict the variability in survival outcome (6–10). They include International Staging System (ISS) stage, Revised International Staging System (RISS) stage, and chromosomal abnormalities detected by conventional karyotyping or fluorescent *in situ* hybridization (FISH) (11). The ISS incorporates serum beta$_2$-microglobulin and serum albumin, which initially emerged as powerful predictors of survival outcome (11). Patients with ISS stage III disease at diagnosis had a median OS of 29 months compared to 44 and 62 months with stage II and stage I disease, respectively. Among the chromosomal abnormalities, t(4;14), t(14;16), t(14;20), del(17p) or chromosome 1 abnormality have been associated with adverse prognosis (2, 12, 13). The RISS has recently been adopted by Internal Myeloma Working Group (IMWG) to risk-stratify patients with multiple myeloma (14). The RISS incorporates high-risk CG abnormalities and elevated LDH into ISS as a three-stage system. According to this staging system, the 5-yr survival rate was 82%, 62%, and 40% in patients with RISS stage I, stage II, and stage III disease, respectively.

The progression-free survival (PFS) in patients with standard-risk disease after an upfront auto-HCT, with or without maintenance, is approximately 36–46 months compared to 18 months in patients with high-risk multiple myeloma (15, 16). We and others have observed that a subset of standard-risk multiple myeloma patients tends to do worse than expected (17, 18). We tried to evaluate the factors associated with inferior outcome in patients with otherwise standard-risk multiple myeloma.

Subjects and methods

We reviewed our database of 1750 patients with multiple myeloma who underwent auto-HCT between October 2002 and April 2010. Of 1750 transplanted patients, 1192 (68%) received auto-HCT in first remission, while the rest of 558 (32%) patients received auto-HCT after salvage therapy for relapsed/refractory disease. Among them, we identified 51 standard-risk multiple myeloma patients, who received upfront auto-HCT and had a PFS of ≤18 months after auto-HCT. These patients were included in the analysis. The PFS cutoff of 18 months was used as it is being used to design clinical trials for salvage therapy in high-risk multiple myeloma patients. Patients with no high-risk cytogenetics such as del (17p13), t(4;14), t(14;16), t(14;20), or chromosome 1 abnormalities identified by conventional karyotyping or FISH and ISS stage I/II were defined as standard-risk multiple myeloma (19). Hematological response (HR) was defined according to the IMWG criteria (20). Hematological response was evaluated before and 100 d after auto-HCT. Overall HR was defined as the sum of stringent complete response (sCR), complete response (CR), very

good partial response (VGPR), and partial response (PR). Concurrent free light-chain amyloidosis (AL) was diagnosed with positive amyloid tissue staining with Congo red stain, immunoglobulin light-chain subtyping, and AL-related organ dysfunction (21). Time to progression was calculated from the time of best HR after 100 d of auto-HCT.

Statistical analysis

The continuous variables were compared by the Student's *t*-test, and categorical variables were compared by chi square or Fisher's exact test. Estimates of survival curves were calculated according to the Kaplan–Meier curve and compared by means of the log-rank test. The Cox proportional hazard regression model was used to assess the relationship between patient characteristics and survival. Only predictive variables with $P < 0.1$ by univariate analysis were considered for multivariate analysis. All reported P values were two-sided, and those <0.05 were considered statistically significant.

Results

The baseline characteristics are summarized in Table 1. The median age was 61 yr (range, 39–76). At diagnosis, the median plasma cells (PCs) percentage in the bone marrow (BM) was 21% (range, 10–90%). Five (11%) patients had concurrent AL. Five (10%) patients had soft tissue plasmacytoma, one each with chest wall, abdominal wall, paraspinal, kidney, and hip muscle plasmacytoma. All 51 patients had diploid karyotype on conventional karyotyping. Among 30 (60%) patients with available FISH analysis at baseline, 26 (87%) patients had no abnormalities, two (5%) patients had monosomy/or deletion 13q (mono/del 13q), two (5%) patients had t(11;14), and one (2%) patient had trisomy 5. Of note, an additional 10 (20%) patients had FISH analysis done on follow-up, which did not show any high-risk chromosomal abnormalities. Immunohistochemistry (IHC) on initial BM apart from CD38/CD138 identified 34 (71%) patients with CD56 positivity, 12 (24%) with CD33, and 11 (23%) with CD20 positivity [≥10% expression by (IHC) was considered positive].

Induction therapy

Thirty (58%) patients received induction with either an IMiD or bortezomib-based regimen, 16 (31%) patients received IMiD + bortezomib, two (4%) patients received conventional chemotherapy (alkylating agent-based regimens), and three (6%) patients did not receive induction chemotherapy before auto-HCT. The median time to auto-HCT was 9.8 months. Sixteen (31%) patients received maintenance therapy after auto-HCT; among them, 11 (69%) patients received lenalidomide (Table 2).

Response and outcome

The overall response rate (sCR + CR + VGPR + PR) was 92% after induction therapy, which improved to 96% after auto-HCT (Table 3). The rate of stringent complete remission (sCR) was improved from 8% before to 23% after auto-HCT. No transplant-related mortality (TRM) was seen in the first 100 d of auto-HCT.

Survival

The median PFS was 7.8 (range, 1.8–18) months, and median OS was 56.3 months (range, 7.2–70.5), with 5-yr OS of 47% (Fig. 1). The median PFS based on ISS staging was 7.5, 7, and 3.7 months for stage I, stage II, and stage III disease, respectively (P = 0.6). The median OS based on ISS staging was 68.8, 49.9, and 41.5 months for stage I, stage II, and stage III disease, respectively (P = 0.5).

On univariate analysis, patients with concurrent AL had significantly inferior PFS 3.7 vs. 8.7 months (HR; 2.61, 95% CI; 0.64–10.58, $P = 0.03$). Patients with BM PCs ≥10% prior to auto-HCT (6.5 vs. 8.5 months, HR: 1.48, 95% CI: 0.64–3.4, $P = 0.37$), pre-auto-HCT hemoglobin <10 g/dL (5.4 vs. 8.7 months, HR; 1.37, 95% CI 0.61–3.06, $P = 0.2$), and ISS stage III disease (6 vs. 7.5 months, HR; 1.04, 95% CI 0.44–2.44, $P = 0.9$) showed a trend toward inferior PFS. Interestingly, age ≥70 yr showed a trend toward a longer PFS (7.6 vs. 5.5 months, HR: 0.68, 95% CI: 0.27–1.74, $P = 0.4$). Patients who received lenalidomide maintenance after auto-HCT also showed a trend toward longer PFS that was not statistically significant (9.4 vs. 7 months, HR; 0.72, 95% CI; 0.37–1.38, $P = 0.2$) (Table 4).

On univariate analysis for OS, occurrence of soft tissue plasmacytoma at the time of diagnosis was associated with a significantly shorter OS (41.5 vs. 68.3 months, HR: 3.05, 95% CI: 0.57–16.29, $P = 0.02$). Patients with BM PCs ≥10% prior to auto-HCT (55.2 vs. 77.5 months, HR: 1.36, 95% CI: 0.65–2.83, $P = 0.4$) and ISS stage III disease (41.5 vs. 68.3 months, HR; 1.56, 95% CI 0.36–6.63, $P = 0.5$) showed a trend toward inferior OS that was not statistically significant. Interestingly, age ≥70 yr (76 vs. 55.2 months, HR; 0.68, 95% CI 0.27–1.74, $P = 0.4$) and CD20 expression on PCs (68.8 vs. 52.6 months, HR; 0.61, 95% CI; 0.26–1.43, $P = 0.3$) showed a trend toward longer OS that did not reach statistical significance. We could not perform multivariate analysis because only one variable analyzed for PFS as well as OS had a P value of <0.1. (Table 5)

Discussion

In this report, we highlighted a subset of standard-risk multiple myeloma patients who received upfront auto-HCT and had a shorter than expected PFS. Among the variables evaluated for inferior PFS, concurrent AL was predictive of inferior PFS, whereas ≥10% PCs in BM prior to auto-HCT and pre-auto-HCT Hb <10 g/dL was suggestive of inferior PFS but not statistically significant.

The aim of this retrospective analysis was to identify factors that may predict the worse outcome in this otherwise standard-risk multiple myeloma patients. The incidence of concurrent AL in patients with multiple myeloma is approximately 10% as reported in retrospective studies (21, 22). Both AL and multiple myeloma are PC disorders but with a different phenotype. Unlike multiple myeloma, AL is characterized by light-chain deposition in tissues, including vital organs of the body that can lead to organ dysfunction and failure if not treated (23). Dinner *et al.* (21) conducted a retrospective analysis, evaluating clinical outcome of multiple myeloma patients with concurrent AL. According to their analysis, survival outcome was similar in patients with concurrent AL and asymptomatic multiple myeloma, but significantly inferior in patients with AL and symptomatic myeloma having

≥10% PCs in BM or lytic bone lesions. In our study, five (11%) patients had concurrent AL with median PCs in BM of 21% (range, 10–50%). Four patients had renal AL, and one had pancreatic AL. Three of these patients received either PI- or IMiD-based induction therapy, and the remaining two did not receive any therapy prior to auto-HCT. Among them, four achieved a HR (n = 1 and 3; VGPR and PR, respectively). However, responses were short-lived with a median PFS of 3.7 months, significantly shorter than the rest of the group. Although the number of patients was small, our finding is still consistent with other reports in the literature (21). Therefore, concurrent AL in patients with multiple myeloma may serve as a useful prognostic marker. Moreover, all of these patients should receive PI- and IMiD-based chemotherapy regimens to improve outcome.

Eleven (23%) patients had CD20-positive myeloma cells in the diagnostic BM, which is consistent with the reported incidence in patients with multiple myeloma (24, 25). Among various molecular entities identified by gene expression profiling in multiple myeloma, CD-2 is one subgroup associated with favorable prognosis. Moreover, CD-2 expression was found to be associated with elevated levels of CD20 expression (26). Although we did not have gene expression profiling data available for our patients, we did notice that CD20 expression was associated with longer PFS and OS on univariate analysis. Studies have also shown positive correlation between CD20 positivity and t(11;14) (q13q32) (25). Of 11 patients with CD 20 positivity, six at diagnosis and three at follow-up had FISH analysis. Only one patient had t(11;14)(q13q32); the rest were negative for any chromosomal abnormality. Treon *et al.* (24) reported efficacy of anti-CD20 monoclonal antibody in multiple myeloma patients expressing CD20. Of note, none of our patient with CD20-positive disease received anti-CD20 monoclonal antibodies. Our findings need to be validated in a larger group of patients.

Advance age is considered a poor prognostic factor in patients with multiple myeloma and is generally associated with advance disease, although advanced age is not considered an exclusion criteria for auto-HCT (27). In our analysis, advanced age (≥70 yr) was not predictive of inferior PFS or OS. Furthermore, no TRM was observed in patients with advanced age. Our data further endorse that the auto-HCT is a feasible option in patients with advanced age. The incidence of soft tissue extramedullary plasmacytoma is 7–18% at diagnosis and around 20% at relapse in patients with multiple myeloma. Usually plasmacytoma is associated with plasmablastic morphology and lacks CD56 expression. Response is poor when treated with conventional approach or thalidomide alone (28). In the studied group, five (10%) patients had soft tissue plasmacytoma; none of the patients had a plasmablastic morphology and three of five lacked CD56 expression. Two patients were treated with IMiD and PI combination, two patients had PI-based regimen and one received IMiD-based regimen followed by auto-HCT. The PFS was not significantly different, but OS was inferior (41.5 vs. 68.3 months, P = 0.02). The clinical outcome of these patients can be improved by high-dose chemotherapy-based regimen followed by auto-HCT.

In this group of standard-risk multiple myeloma patients, the median PFS was 7.8 months and OS 56.3 months, which is significantly inferior for patients with standard-risk disease, considering 90% of patients received induction therapy with novel agents (bortezomib and/or IMiD) and underwent upfront auto-HCT. In fact, PFS is similar to the patients with

high-risk multiple myeloma (29). Our analysis suggests a need for better diagnostic modalities that have a potential to identify patient with high-risk disease not recognized by established methods. Gene expression profiling (GEP) offers a possible solution with better test sensitivity and specificity (30). However, GEP was not uniformly available during the time period of this study, as is available now. The heterogeneity in clinical outcome of multiple myeloma, even in patients with similar risk disease, warrants better tools for risk stratification, possibly by incorporating GEP or next-generation sequencing (NGS) with revised ISS (31). Furthermore, refining response criteria with inclusion of minimal residual disease assessment in the existing response criteria will help to better assess the disease status and durability of responses for planning further treatment strategies.

We acknowledge the limitations of retrospective nature of our study, including selection bias and small sample size. Second, it is possible that some patients treated earlier might not have been screened for high-risk cytogenetic features by FISH analysis and mislabeled as having standard-risk disease. Although 90% of the patients received induction therapy with an IMiD, bortezomib-based regimen, or a combination of IMiD and bortezomib, it is important to highlight that only 31% of patients received PI and IMiD combination upfront, which is now standard of care for standard-risk multiple myeloma. This might be one of the reasons for an inferior outcome. Nevertheless, our study identified variables that can be potentially combined with more sensitive diagnostic methods to identify high-risk multiple myeloma patients. These patients may then be treated as high-risk patients to achieve a better outcome.

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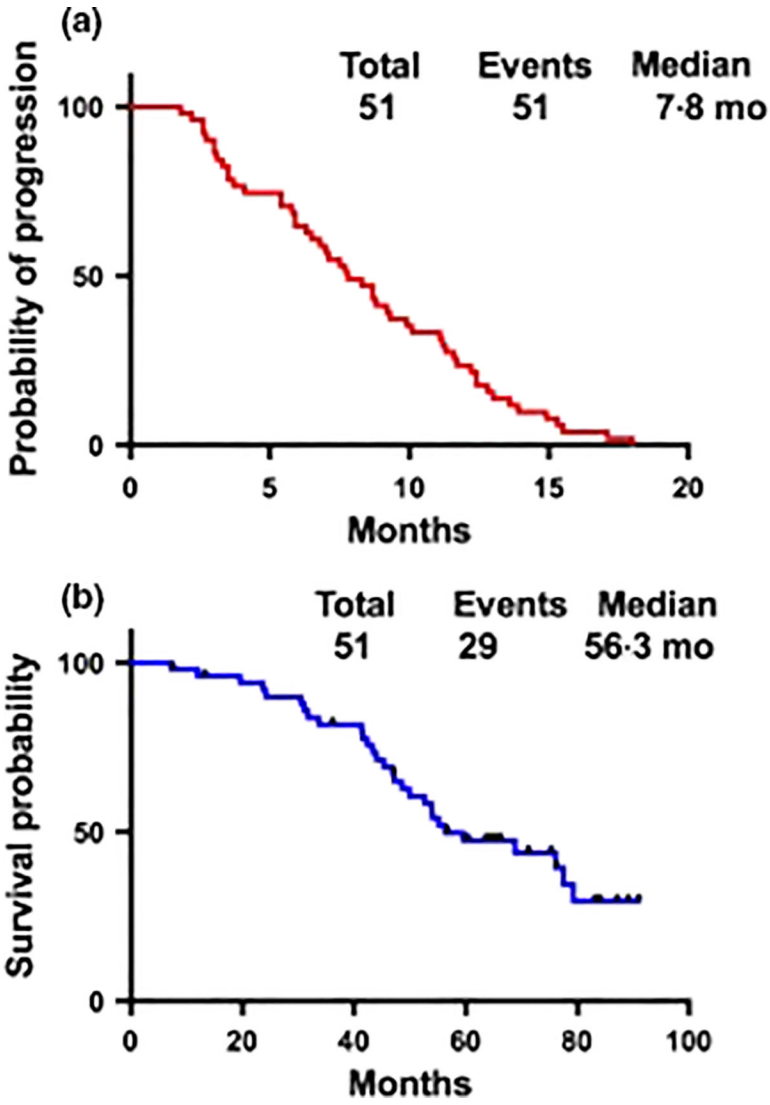

Figure 1.

(a) Progression-free survival (b) Overall survival curves for all patients according to the Kaplan–Meier product limit method and compared by means of the log-rank test.

Table 1

Baseline characteristics

Characteristics	Median [range] or *N* (%)
Age, yr	61 [39–76]
Hemoglobin (g/dL)	11 [6.4–15.7]
Cr (mg/dL)	1.1 [0.6–3.7]
Albumin (g/dL)	3.4 [2.1–4.9]
β2-microglobulin	3 [1.4–14.8]
Plasma cell BM	21 [10–90]
S. Calcium	9.1 [7.4–10.2]
Immunoglobulin subtype	
IgG	28 (55)
IgM	1 (2)
IgA	13 (25)
Light chain only	7 (14)
Concurrent amyloidosis	5 (11)
Soft tissue plasmacytoma	5 (10)
Durie Salmon Stage I	15 (28)
Durie Salmon Stage II	39 (72)
International Staging System[1]	
Stage I	15 (35)
Stage II	22 (51)
Stage III	6 (14)
FISH[2]	
Negative	26 (87)
Monosomy 13/del 13	2 (5)
t (11;14)	2 (5)
Trisomy 5	1 (2)
Immunophenotype	
CD56 (>10%)	34 (71)
CD20 (>10%)	11 (23)
CD33 (>10%)	12 (24)
SPEP	1.7 [0–38]
BJP (mg/TV)	6 [0–1000]
Immunofixation positive for monoclonal proteins	40 (98)
Time to auto-HCT from (months)	9.8 [3.8–56.9]

Cr, creatinine; SPEP, serum protein electrophoresis; BJP, bence jones protein; FISH, fluorescent *in situ* hybridization.

[1] 43 (84%) were evaluable for ISS staging.

[2] 30 (60%) were evaluable for FISH analysis.

Table 2

Type of induction regimens, [*N* (%)]

IMiD-based regimen	15 (29)
PI-based regimen	15 (29)
IMiD + PI-based regimen	16 (31)
Conventional chemotherapy	2 (4)
No induction treatment	3 (6)
Maintenance therapy after auto-HCT	16 (31)

IMiD, immunomodulatory drugs (lenalidomide or thalidomide); PI, proteasome inhibitors; auto-HCT, autologous hematopoietic stem cell transplant; conventional, alkylating agent or steroid based therapy.

Table 3

Hematological responses [*N* (%)]

Response	Prior to auto-HCT	After auto-HCT
Overall	47 (92)	49 (96)
sCR	4 (8)	13 (23.5)
CR	4 (8)	5 (10)
VGPR	7 (14)	11 (22)
PR	32 (63)	20 (39)

Overall response, sCR + CR + VGPR + PR; CR, complete response; sCR, stringent CR; VGPR, very good partial response; PR, partial response; auto-HCT, autologous hemopoietic stem cell transplant.

Table 4

Univariate and multivariate analyses for progression-free survival

	Univariate			
Variables	**PFS (months)**	**HR**	**95% CI**	***P***
Age > 70 yr	7.6 vs. 5.5	0.68	0.27–1.74	0.4
ISS stage III	6.0 vs. 7.5	1.04	0.44–2.44	0.9
CD 20 expression (>10%)	8.7 vs. 7.6	0.74	0.39–1.39	0.3
CD 33 expression (>10%)	7.25 vs. 7.8	1.11	0.58–2.09	0.7
Concurrent amyloidosis	3.7 vs. 8.7	2.51	0.64–10.58	0.03
Pre-TP Hb < 10 g/dL	5.4 vs. 8.7	1.37	0.61–3.06	0.3
Pre-TP plasma cells > 10% in BM	6.5 vs. 8.5	1.48	0.64–3.4	0.2
Soft tissue plasmacytoma	11.1 vs. 7.8	0.68	0.37–1.25	0.7
Induction therapy with novel agents	8.7 vs. 7.7	0.50	0.17–1.84	0.2
Revlimid maintenance post-auto-HCT	10.1 vs. 7.2	0.68	0.37–1.25	0.2

HR, hazard ratio; CI, confidence interval; ISS, International Staging System for multiple myeloma; Pre-TP, prior to autologous hematopoietic stem cell transplant; Hb, hemoglobin; BM, bone marrow; Novel agents, Immunomodulators and or proteosome inhibitor-based regimens; auto-HCT, autologous hemopoietic stem cell transplant; PFS, progression-free survival.

Table 5

Univariate for overall survival

Variables	OS (months)	HR	95% CI	*P*
Age > 70 yr	76 vs. 55.2	0.68	0.27–1.74	0.4
ISS stage III	41.5 vs. 56.3	1.56	0.36–6.63	0.5
CD 20 expression	68.8 vs. 52.6	0.61	0.26–1.43	0.31
Concurrent amyloidosis	NR vs. 45.3	0.77	0.19–2.9	0.7
Soft tissue plasmacytoma	41.5 vs. 68.3	3.05	0.57–16.29	0.02
Initial Hb < 10 g/dL	69.5 vs. 53.9	0.71	0.29–1.77	0.5
Plasma cells > 20% in BM[1]	55.2 vs. 77.5	1.36	0.65–2.83	0.4

HR, hazard ratio; CI, confidence interval; ISS, International Staging System for multiple myeloma; Hb, hemoglobin; BM, bone marrow; OS, overall survival.

[1]On initial BM evaluation.