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Prognostic factor analyses of myeloma survival with intergroup trial S9321 (INT 0141): examining whether different variables govern different time segments of survival

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Abstract

Multiple myeloma (MM) survival plots usually display steeper initial and shallower subsequent slopes reflecting differences in disease biology and likely prognostic factors (PF). S9321 trial was selected to determine PF operative at baseline and subsequent 3, 4, 5, and 7-year landmarks (LM-0, LM-3, LM-4, LM-5, and LM-7). With a median follow-up of 8.2 years, survival was similar in transplant and standard therapy arms, justifying data pooling. Median survival for 775 eligible patients is 48 months. According to proportional hazards models, seven of 12 investigated baseline variables retained independent significance for LM-0, of which only two (beta-2-microglobulin and age) extended out to LM-7; the remaining five comprised features of disease aggressiveness (lactate dehydrogenase, calcium, platelet count, C-reactive protein) and host comorbidity (performance status). Our observations of LM dependency of PF can be exploited toward advancing myeloma therapy by stratifying patients according to whether early or late portions of the survival history are being targeted.

Keywords

Myeloma; Transplant trials; IFM trials; Total therapy trials; SWOG 9321

Introduction

The prognosis of patients afflicted with multiple myeloma (MM) varies widely and depends on baseline laboratory features related to tumor burden [bone marrow plasmacytosis, anemia, extent of bone disease, beta-2-microglobulin (B2M)], disease aggressiveness [lactate dehydrogenase (LDH); the presence of cytogenetic abnormalities (CA) and, more recently, molecular genetics such as interphase fluorescence in situ hybridization (FISH) and

gene expression profiling (GEP); cytokine activity such as interleukin-6 (IL6) reflected by levels of C-reactive protein (CRP) and albumin], and host features [age, performance status (PS), renal and cardio-pulmonary functions which can be aggravated by M-protein products causing AL or light chain deposition disease] (for review, see [1,2]). The recently introduced International Staging System (ISS) classification combining serum levels of B2M and albumin has been widely adopted [3] and has replaced the first staging system named after Durie and Salmon [4]. Still, within tumor stages, considerable variation remains in clinical outcomes which have been extended markedly over the past 5 to 10 years as a result of autotransplant-supported high-dose melphalan treatment [5–9] and the more recent introduction of novel agents such as thalidomide, lenalidomide, and bortezomib employed together with dexamethasone, each other, and with standard genotoxic agents [10–14].

Kaplan–Meier survival plots often follow biphasic or triphasic patterns, raising therefore the issue as to whether different baseline parameters might govern the different time segments of survival outcomes. Here we have examined survival outcomes on Inter-group trial INT-141 [Southwest Oncology Group (SWOG) protocol S9321] [15] according to different landmarks to investigate whether the differently shaped segments of the overall survival curves are “governed” by different sets of baseline variables.

Patients and methods

The protocol details of S9321 have been updated recently [16], and the median follow-up is now 8.2 years. As the two randomized study arms (standard chemotherapy, single autotransplant) exhibited super-imposable overall survival curves, they were collapsed for the purpose of this investigation. Patients on the allotransplant arm were excluded. Survival curves were generated using the product-limit method [17] and univariate and multivariate regression analyses were performed using the Cox proportional hazards model [18], with baseline prognostic factors dichotomized at established cut-points. A recently developed method for deciding on the number of exponential curves that best fit an observed survival curve, and the placements of the change-points for those exponentials [19], was used to influence the best landmark values for further analyses. Hazard ratios over time were estimated by dividing estimates of hazard rates [20] for those over and under prognostic factor cut-points. The protocol had been reviewed and approved by individual institutional review boards. All patients had signed a written informed consent before protocol enrollment, in keeping with the Helsinki Declaration.

Results

Overall survival, portrayed in Fig. 1, is characterized by slope segments with progressively decreasing steepness, herein modeled for OS by two such segments with a change-point at 52 months, justifying the analyses of serial LM. Univariately significant laboratory variables associated with OS varied with the LM examined (Table 1). Of 12 baseline parameters examined, 10 affected survival significantly in the context of LM-0, with only trends observed for albumin (constituting ISS stage together with B2M) and osteolytic bone lesions (component of the Durie–Salmon staging system). B2M impacted survival from all LM while the prognostic implications of CRP, platelet count, hemoglobin, calcium, and performance status were restricted to LM-0. Age affected prognosis from LM-0, LM-3, LM-4, and LM-7 and LDH from LM-0 and LM-5. In the multivariate model (Table 2), B2M's consistent survival impact across all LM was confirmed while, of the seven LM-0-significant baseline variables, five did not extend beyond LM-0; older age appeared significant for LM-3 and LM-7 with a strong trend for LM-4. According to R^2 statistics, values of nearly 18% and 19%, respectively, for LM-0 and LM-7 suggest that almost 20% of variability in survival outcome can be accounted for. In the case of the other intervening LM

analyses, R^2 values of less than 10% reflect a relatively poor performance of the multivariate models pertaining to these time segments. Similar conclusions were reached using continuous as opposed to dichotomized cut-points for prognostic factors (data not shown).

To illustrate the impact of the LM variable, Fig. 2 portrays hazard ratio (HR) estimates over time. With the exception of age, HR values declined over time, especially for PS and platelet count. The consistently significant adverse impact of B2M across all LM considered was also reflected in the shallower decline of its HR values. Figure 3 portrays Kaplan–Meier plots dated from early to later LM relevant to the presence of two variables shown to govern all segments of survival history (B2M, age) or LM-0 only (calcium, LDH). In the case of B2M and age, the risk factor number-dependent progressively shorter survival pertained across LM (left panels) whereas, for calcium and LDH, such prognostic discrimination was lost beyond LM-0 (right panels).

Discussion

To our knowledge, this is the first report to have examined the issue of whether different baseline prognostic variables “govern” different portions of Kaplan–Meier survival plots. Applying progressively increasing LM from LM-0 to LM-7 in this protocol with a median follow-up of live patients of 8.2 years, we indeed discovered that of seven independently significant parameters affecting survival when examined from LM-0, only two carried forward to later LM (B2M and age). Thus, the rapid loss of prognostic implications from LM-3 onward of calcium, LDH, CRP, platelet count, and performance status is consistent with a rapid attrition of such patients due to disease aggressiveness (calcium, LDH, CRP, platelet count) or co-morbidities (reflected in the performance status). Conversely, B2M governed all phases of the survival curve, reflecting the importance of initial tumor burden (and yet uncovered mechanisms) for the entire patient lifespan.

Conclusion

Multiple myeloma survival plots usually display steeper initial and shallower subsequent slopes, reflecting differences in disease biology, which in turn may be governed by different baseline prognostic factors. Applying serial landmark techniques to 775 newly diagnosed patients enrolled in SWOG trial S9321 with a median follow-up of more than 8 years, LDH and calcium governed the early survival phase, while B2M was the sole feature that retained independent significance for later survival from 3, 4, 5, and 7-year landmarks.

We are presently investigating whether such LM-dependent prognostic variables also apply to more contemporary and overall more effective therapies as our Total Therapy 2 and 3 protocols [8,9]. Consideration of potentially LM-dependent variables in clinical trial design should aid in identifying therapeutic interventions specifically targeting LM-0-restricted highly aggressive disease, while reserving longer outcome-targeting strategies, such as reducing tumor burden, to later phases of therapy.

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Fig. 1.
Overall survival from registration to start of protocol therapy. Overall survival fit with two exponentials with a cut-point at 52 months

Fig. 2.
Hazard ratio (*HR*) values of the significant prognostic factors (*PF*) are portrayed over time

Fig. 3.

Kaplan–Meier plots from treatment initiation according to two variables affecting different segments of survival: *Left panels* serum B2M and age affected survival independently across all landmarks (LM) examined; the best outcome was observed when both variables were $u \leq 3.5$ mg/L and declined progressively in the presence of one and especially two adverse features. *Right panels* serum LDH and calcium levels affected survival independently only from baseline (LM-0); hypercalcemia imparted short survival regardless of lactate dehydrogenase (LDH) level, resulting in three risk groups with significantly varying outcomes; in the presence of 0 adverse variables, survival was superior and declined progressively in the presence of one and two adverse features

Table 1

Univariate analysis: results of parameters associated with overall survival applying landmarks at baseline (LM-0) and at 3, 4, 5, and 7 years after treatment start (LM-3, LM-4, LM-5, LM-7)

Variable	n/N (%) (baseline)	OS from LM-0		OS from LM-3		OS from LM-4		OS from LM-5		OS from LM-7	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age >60 years	173/775 (22%)	1.47 (1.21, 1.78)	<0.001	1.58 (1.19, 2.11)	0.002	1.61 (1.13, 2.29)	0.008	1.44 (0.93, 2.24)	0.101	2.88 (1.62, 5.12)	<0.001
CRP ≥8 mg/L	225/704 (32%)	1.48 (1.23, 1.77)	<0.001	1.16 (0.87, 1.54)	0.311	1.30 (0.94, 1.81)	0.116	1.27 (0.86, 1.87)	0.228	1.34 (0.76, 2.37)	0.307
Platelet count <130,000/μL	100/767 (13%)	1.98 (1.57, 2.49)	<0.001	1.37 (0.89, 2.10)	0.148	1.01 (0.56, 1.82)	0.969	0.90 (0.44, 1.84)	0.774	1.25 (0.50, 3.12)	0.632
Hemoglobin <10 g/dL	364/768 (47%)	1.48 (1.25, 1.75)	<0.001	1.20 (0.94, 1.54)	0.135	1.05 (0.78, 1.41)	0.745	1.10 (0.78, 1.55)	0.590	1.21 (0.74, 1.99)	0.449
Albumin <3.5 g/dL	264/759 (35%)	1.16 (0.97, 1.38)	0.097	1.08 (0.83, 1.40)	0.562	1.03 (0.75, 1.41)	0.870	0.87 (0.59, 1.27)	0.468	0.92 (0.53, 1.59)	0.771
Serum B2M >3.5 mg/L	370/730 (51%)	1.73 (1.45, 2.05)	<0.001	1.49 (1.16, 1.91)	0.002	1.42 (1.06, 1.92)	0.020	1.42 (1.00, 2.00)	0.049	1.83 (1.11, 3.02)	0.017
Calcium ≥10 mg/dL	164/763 (21%)	1.50 (1.24, 1.82)	<0.001	1.22 (0.89, 1.68)	0.218	1.08 (0.72, 1.61)	0.719	1.13 (0.71, 1.80)	0.615	0.91 (0.43, 1.92)	0.808
Creatinine >2 mg/dL	128/765 (17%)	1.92 (1.55, 2.37)	<0.001	0.98 (0.64, 1.49)	0.913	0.92 (0.55, 1.54)	0.750	0.94 (0.52, 1.71)	0.847	1.28 (0.58, 2.81)	0.545
LDH ≥190 U/L	316/738 (43%)	1.47 (1.24, 1.74)	<0.001	1.31 (1.02, 1.68)	0.034	1.28 (0.94, 1.72)	0.113	1.12 (0.78, 1.60)	0.553	0.85 (0.49, 1.48)	0.570
Performance status 1+	145/759 (19%)	1.58 (1.32, 1.89)	<0.001	1.10 (0.86, 1.40)	0.454	1.00 (0.75, 1.34)	0.989	1.05 (0.75, 1.48)	0.768	1.00 (0.61, 1.63)	1.000
ISS stage 3	216/722 (30%)	1.70 (1.42, 2.04)	<0.001	1.25 (0.93, 1.67)	0.139	1.07 (0.74, 1.53)	0.732	1.08 (0.71, 1.65)	0.712	1.58 (0.91, 2.74)	0.103
>3 Lytic bone lesions	381/764 (50%)	1.14 (0.96, 1.34)	0.133	1.04 (0.82, 1.32)	0.751	1.10 (0.82, 1.47)	0.527	1.04 (0.74, 1.46)	0.807	1.07 (0.66, 1.76)	0.777

HR hazard ratio, 95% CI 95% confidence interval, P value from Wald chi-square test in Cox regression

Table 2

Multivariate analysis: results of parameters associated with overall survival applying landmarks at baseline (LM-0) and at 3, 4, 5, and 7 years after treatment start (LM-3, LM-4, LM-5, LM-7)

Variable	OS from LM-0 (N=625)		OS from LM-3 (N=376)		OS from LM-4 (N=376)		OS from LM-5 (N=376)		OS from LM-7 (N=213)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age >60 years	1.40 (1.13, 1.74)	0.002	1.46 (1.04, 2.05)	0.027	1.51 (0.99, 2.28)	0.053	1.28 (0.76, 2.15)	0.349	2.52 (1.24, 5.10)	0.010
CRP ≥ 8 mg/L	1.29 (1.05, 1.57)	0.013	1.15 (0.84, 1.56)	0.386	1.34 (0.93, 1.91)	0.112	1.23 (0.81, 1.87)	0.341	1.60 (0.87, 2.97)	0.133
Platelet count <130,000/μL	1.54 (1.18, 2.01)	0.001	1.13 (0.70, 1.82)	0.624	0.92 (0.49, 1.72)	0.791	0.74 (0.34, 1.62)	0.454	0.87 (0.33, 2.27)	0.778
Serum B2M >3.5 mg/L	1.48 (1.22, 1.79)	<0.01	1.52 (1.16, 2.01)	0.003	1.54 (1.11, 2.14)	0.009	1.56 (1.07, 2.28)	0.022	2.24 (1.27, 3.94)	0.005
Calcium ≥ 10 mg/dL	1.34 (1.08, 1.68)	0.008	1.32 (0.92, 1.88)	0.127	1.22 (0.78, 1.91)	0.380	1.35 (0.82, 2.24)	0.243	1.13 (0.49, 2.57)	0.779
LDH ≥ 190 U/L	1.28 (1.06, 1.55)	0.010	1.22 (0.92, 1.62)	0.176	1.20 (0.85, 1.69)	0.296	1.10 (0.74, 1.64)	0.641	0.72 (0.38, 1.38)	0.324
Performance status 1+	1.33 (1.08, 1.63)	0.007	0.92 (0.69, 1.21)	0.540	0.85 (0.61, 1.19)	0.343	1.00 (0.68, 1.48)	0.992	1.07 (0.61, 1.87)	0.820
R ² value	17.68%		7.78%		8.55%		6.54%		19.03%	

HR hazard ratio, 95% CI 95% confidence interval, P value from Wald chi-square test in Cox regression