Complete remission in multiple myeloma examined as time-dependent variable in terms of both onset and duration in Total Therapy protocols

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Landmark analyses are used to investigate the importance for survival of achieving complete response (CR), an important initial goal of myeloma therapy. With median times to CR in Total Therapy (TT) trials of approximately 1 year, this approach excludes a sizeable fraction of patients dying before such a landmark. To permit inclusion of all trial participants, we investigated the prognostic implications of both onset and duration of CR as time-dependent variables. Superseding the adverse effects of cytogenetic abnormalities and other standard prognostic parameters, both failure to achieve CR (non-CR) and, especially, loss of CR (los-CR) were independently associated with inferior survival in TT1, TT2, and TT3 protocols. In the context of gene array–defined risk, available in TT2 and TT3 subsets, both los-CR and non-CR terms were retained in the survival model as dominant adverse variables, stressing the prognostic importance of sustaining CR status, especially in high-risk disease. (Blood. 2009;114:1299-1305)

Introduction

As result of a substantial increase in the rate of complete response (CR)[1,2] from less than 5% to more than 60%, the median myeloma survival has been significantly extended from less than 3 years with standard melphalan-prednisone to more than 10 years on the experimental arm of Total Therapy 2 (TT2) with thalidomide.[3] Recent reports of novel agent combination trials using immunomodulatory agents (thalidomide or lenalidomide), together with bortezomib or melphalan, have demonstrated CR rates as high as 40% without resorting to transplantation.[4-6] Follow-up time, however, is too short to judge the long-term efficacy of such novel therapies.

In addressing the fallacies of CR,[7] we noted that a fraction of 10-year survivors had never achieved CR,[8] which was attributed to myeloma evolving from a smoldering phase[9] or having gene expression profiling (GEP) characteristics of monoclonal gammopathy of undetermined significance (MGUS).[10] Conversely, high CR rates, especially in GEP-defined high-risk myeloma, were critical to extended survival.[11] In the context of TT2, the median survival of the 15% with high-risk myeloma was only 2 years as opposed to longer than 10 years in the remainder.[12] Sustaining CR status for at least 3 years (sus-CR) was associated with superior survival versus not achieving CR (non-CR) and especially attaining and losing CR (los-CR).[13] Patients not surviving the 3-year landmark had to be dropped from the analysis. Here we examine a different statistical approach that accounts for all patients and permits investigation of prognosis in the context of precise timing of onset and loss of CR. By applying time-dependent variable status to posttreatment events, such as achieving CR status or losing such designation, the full complexity of CR and its duration can be examined in patients with high-risk myeloma who, despite high CR rates, often have a short survival as a result of rapid disease recurrence.

Methods

The details of TT1, TT2, and TT3 regimens have been published previously.[3,14-17] All protocols had been approved by the Institutional Review Board of the University of Arkansas, and all patients had signed a written informed consent acknowledging the investigational nature of the trials and appreciating the existence of other treatment options, in accordance with Food and Drug Administration guidelines and the Declaration of Helsinki. Nearly 70% of all charts had been reviewed by independent auditor teams, verifying protocol compliance as well as efficacy and toxicity data.

GEP analyses were performed to define molecular subgroups,[18] prognostic risk,[12] and MGUS likeness.[19]

Our continuously updated multiple myeloma database was interrogated to determine, among 231 patients enrolled in TT1, 668 patients accrued to TT2, and 303 to TT3, the timing of onset of stringently defined CR.[1,2] CR duration was measured from its onset until the recurrence of the original monoclonal protein, documented by immunofixation analysis on at least 2 successive occasions at least 2 months apart. Relapse from CR was defined as persistent reemergence, on at least 3 successive occasions over the course of 3 months, of the original monoclonal band on immunofixation analysis; other criteria of relapse from CR included the documentation of serum-M or urine-M on standard electrophoresis, recurrence or increase in monoclonal bone marrow plasmacytosis to greater than 10%, development of cytogenetic abnormalities (CAs), or of imaging abnormalities, such as focal lesions on magnetic resonance imaging or positron emission tomography scans.

We then applied multivariate Cox regression modeling[20] to determine which baseline parameters, along with time-dependent onset of and duration of CR, significantly affected overall survival. Treating onset and duration of CR as time-dependent variables[21] in the Cox regression models enabled us to analyze the impact of these outcomes on the entire population, unlike landmarking techniques, which only consider a subset of the population. Stepwise selection and Cox proportional hazard regression modeling were applied to the multivariate analyses. Kaplan-Meier methods were used to generate survival distribution graphs,[22] and comparisons were

Submitted March 18, 2009; accepted June 2, 2009. Prepublished online as *Blood* First Edition paper, June 11, 2009; DOI 10.1182/blood-2009-03-211953.

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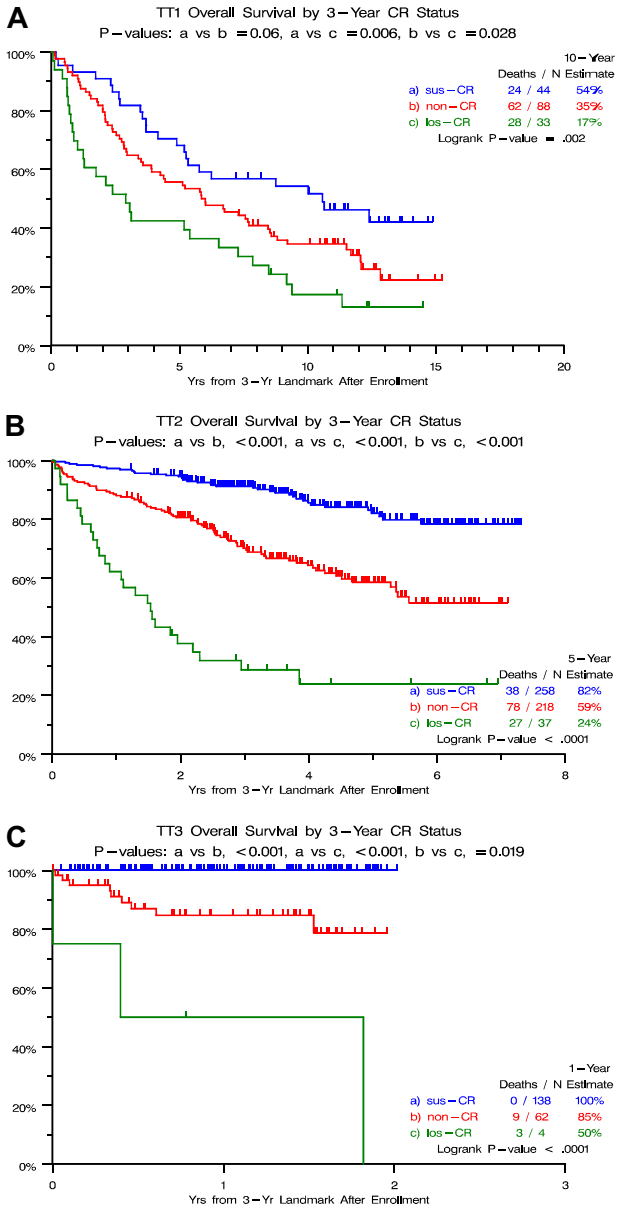

Figure 1. Overall survival by 3-year CR status. (A) For TT1, survival was superior in case complete response (CR) status had been sustained for 3 years (sus-CR), compared with not having attained CR (non-CR) and especially to having attained and lost CR (los-CR) within the 3-year time frame. (B) For TT2, survival was superior in case complete response (CR) status had been sustained for 3 years (sus-CR), compared with not having attained CR (non-CR) and especially to having attained and lost CR (los-CR) within the 3-year time frame. (C) For TT3, survival was superior in case complete response (CR) status had been sustained for 3 years (sus-CR), compared with not having attained CR (non-CR) and especially to having attained and lost CR (los-CR) within the 3-year time frame.

made using the log-rank test.[23] Categorical comparisons were made using the χ^2 test.[24]

Results

Figure 1 depicts survival outcomes according to CR categories from a 3-year landmark after initiation of TT1 (Figure 1A), TT2 (Figure 1B), and TT3 protocols (Figure 1C). In all 3 trials, survival was particularly poor in the los-CR category, and non-CR was significantly inferior to sus-CR in TT2 and TT3. These marked survival differences could be traced to differences in baseline characteristics (Table 1), which were least favorable in the los-CR category, in which high lactate dehydrogenase (LDH) was overrepresented in TT1 (36% vs 16% in sus-CR vs 14% in non-CR; $P = .015$) and TT2 (46% vs 30% in sus-CR vs 21% in non-CR; $P = .003$). In TT2, albumin less than 3.5 g/dL and beta-2-microglobulin (B2M) more than 3.5 mg/L were present in 30% and 51%, respectively, of los-CR patients, compared with 14% and 31% in sus-CR and 16% and 34% in non-CR ($P = .043$, $P = .043$). In TT3, B2M more than 5.5 mg/L and creatinine more than 2 mg/dL were observed in 50% and 25%, respectively, of patients with los-CR compared with 12% and 3% in sus-CR and 24% and 15% in non-CR ($P = .022$, $P = .004$). With access to GEP risk information, available for 273 patients on TT2 and 185 patients on TT3 protocols, high-risk designation was present in 22% and 67% of los-CR versus 8% and 10% of sus-CR versus 3% and 9% in non-CR ($P = .005$, $P = .005$). Similarly, the MF (MAF/MAFB) subgroup was overrepresented in the los-CR (17% and 67%) compared with sus-CR (4% and 7%) and non-CR (3% and 7%; $P = .047$, $P < .001$).

We then examined the time dependence of achieving and losing CR status for the entire population of each TT protocol in the context of baseline variables (Table 2). According to multivariate analyses, in the absence of GEP data, los-CR was the dominant variable associated with inferior survival, regardless of protocol, with hazard ratio (HR) values of 7.71 in TT1 ($P < .001$), 8.89 in TT2 ($P < .001$) and 23.01 in TT3 ($P < .001$; Table 2). Non-CR was also associated with inferior prognosis in all 3 trials, as was the presence of CA. High LDH imparted short survival in TT2 and TT3. In the context of GEP data, available together with all other variables in 334 patients of TT2 and 274 of TT3, los-CR and non-CR both retained independent adverse consequences in both TT2 and TT3. MGUS-like myeloma and both HY (hyperdiploidy) and LB (low bone disease) subgroups implied good prognosis in TT2, whereas no molecular subgroup was found to be significant in TT3. In both trials, high-risk status, the presence of CA, and elevated LDH levels retained independent adverse consequences for survival. A combined look at all 3 protocols in the context of standard variables only revealed that both los-CR and non-CR survived the multivariate model with higher HR values than observed for the remaining independently significant variables such as CA, B2M, creatinine, LDH, and C-reactive protein (CRP; Table 3). In the context of GEP data, available for TT2 and TT3 protocols, both los-CR and non-CR were associated with higher HR values than GEP-defined high risk. MGUS-like myeloma and both HY and LB subgroups implied good prognosis, whereas high LDH and presence of CA conferred short survival.

The relapse kinetics in the first 3 months of documentation of relapse from CR had opposite implications for urine-M and serum-M categories. Those with higher levels of urine-M (> 300 mg/day) had a median postrelapse survival (PRS), measured from a 90-day landmark, of only 1 year as opposed to 3 years for the patients with slower relapse kinetics ($P < .001$; Figure 2A). In the case of serum-M, higher levels (> 1.5 g/dL) were favorable ($P = .06$; Figure 2B). When put into the context of GEP-defined risk, higher urine-M levels observed in the first 3 months after relapse documentation conferred shorter PRS in both low- and high-risk GEP groups (Figure 2C), whereas, in the case of serum-M, higher levels favored longer PRS in the high-risk group ($P = .003$; Figure 2D). We interpret these data as being consistent with urine-M secretion representing less and serum-M more differentiated disease relapse. Analysis of hazard rates over time

Table 1. Baseline characteristics of patients enrolled in TT1, TT2, and TT3 according to response category*

	TT1				TT2				TT3			
Factor	**sus-CR**	**los-CR**	**non-CR**	***P***	**sus-CR**	**los-CR**	**non-CR**	***P***	**sus-CR**	**los-CR**	**non-CR**	***P***
Age ≥ 65 y	3/44 (7)	0/33 (0)	8/88 (9)	.203	42/258 (16)	10/37 (27)	44/218 (20)	.224	33/138 (24)	0/4 (0)	20/62 (32)	.225
Albumin < 3.5 g/dL	9/44 (20)	7/33 (21)	26/88 (30)	.434	35/257 (14)	11/37 (30)	35/216 (16)	.043	21/138 (15)	0/4 (0)	12/62 (19)	.515
B2M ≥ 3.5 mg/L	12/44 (27)	14/33 (42)	32/86 (37)	.350	79/258 (31)	19/37 (51)	75/218 (34)	.043	55/138 (40)	2/4 (50)	27/62 (44)	.830
B2M > 5.5 mg/L	6/44 (14)	2/33 (6)	13/86 (15)	.412	37/258 (14)	9/37 (24)	32/218 (15)	.275	17/138 (12)	2/4 (50)	15/62 (24)	.022
CRP ≥ 4 mg/L	17/43 (40)	18/33 (55)	29/84 (35)	.138	144/255 (56)	24/37 (65)	105/213 (49)	.118	78/138 (57)	4/4 (100)	33/61 (54)	.200
CRP ≥ 8 mg/L	11/43 (26)	10/33 (30)	19/84 (23)	.685	111/255 (44)	15/37 (41)	68/213 (32)	.035	39/138 (28)	2/4 (50)	19/61 (31)	.610
Creatinine ≥ 2 mg/dL	3/44 (7)	1/33 (3)	8/88 (9)	.515	22/251 (9)	3/36 (8)	16/214 (7)	.880	4/138 (3)	1/4 (25)	9/62 (15)	.004
LDH ≥ 190 U/L	7/43 (16)	12/33 (36)	12/88 (14)	.015	77/257 (30)	17/37 (46)	46/217 (21)	.003	29/138 (21)	2/4 (50)	15/62 (24)	.366
CAs†	10/43 (23)	11/33 (33)	24/79 (30)	.588	54/257 (21)	9/37 (24)	59/214 (28)	.252	41/138 (30)	1/4 (25)	14/61 (23)	.612
GEP high-risk	NA	NA	NA	NA	11/139 (8)	4/18 (22)	3/116 (3)	.005	12/124 (10)	2/3 (67)	5/58 (9)	.005
GEP CD-1 subgroup	NA	NA	NA	NA	13/139 (9)	2/18 (11)	4/116 (3)	.141	8/124 (6)	1/3 (33)	1/58 (2)	.041
GEP CD-2 subgroup	NA	NA	NA	NA	17/139 (12)	0/18 (0)	21/116 (18)	.085	7/124 (6)	0/3 (0)	11/58 (19)	.016
GEP HY subgroup	NA	NA	NA	NA	37/139 (27)	3/18 (17)	41/116 (35)	.145	36/124 (29)	0/3 (0)	20/58 (34)	.391
GEP LB subgroup	NA	NA	NA	NA	16/139 (12)	0/18 (0)	11/116 (9)	.300	15/124 (12)	0/3 (0)	8/58 (14)	.764
GEP MF subgroup	NA	NA	NA	NA	6/139 (4)	3/18 (17)	4/116 (3)	.047	9/124 (7)	2/3 (67)	4/58 (7)	<.001
GEP MS subgroup	NA	NA	NA	NA	9/139 (6)	3/18 (17)	16/116 (14)	.103	15/124 (12)	0/3 (0)	7/58 (12)	.814
GEP MY subgroup	NA	NA	NA	NA	27/139 (19)	5/18 (28)	15/116 (13)	.185	23/124 (19)	0/3 (0)	6/58 (10)	.275
GEP PR subgroup	NA	NA	NA	NA	14/139 (10)	2/18 (11)	4/116 (3)	.106	11/124 (9)	0/3 (0)	1/58 (2)	.170
GEP MGUS-like	NA	NA	NA	NA	45/139 (32)	2/18 (11)	44/116 (38)	.076	32/124 (26)	1/3 (33)	15/58 (26)	.958

Values are n/N (%), where n is number with factor and N is number with valid data for factor. NA indicates not applicable.

*CR indicates complete response; sus-CR, attained and sustained through at least 3 years; los-CR, attained and lost in 3 years; non-CR, never obtained response in 3 years.

†CAs at any time before enrollment.

for low-risk and high-risk disease in TT2 and TT3 trials revealed a steep decline in high-risk myeloma to levels of low-risk disease, approximately 5 years for TT2 and 4 years for TT3 (Figure 3).

Discussion

We have previously addressed the issue of prognostic implications of CR in myeloma. CR was not critical to the outcomes of patients with a documented preceding course of smoldering disease[25] or with an MGUS-like GEP signature,[18] but was of great prognostic importance in the setting of GEP-defined high-risk myeloma.[11] The topic was also the subject of 2 Inside *Blood* commentaries[7,26] and a letter to the editor of *Leukemia*.[27] Here we have addressed, for the first time, the importance not only of attaining CR per se but also the issues of timing of onset and duration of CR. Applying time-dependent variable methodology permitted the inclusion of all trial subjects. Independent of traditional prognostic baseline parameters (CA, LDH, B2M, albumin) and even GEP-defined high-risk designation, survival was dominantly favorably affected both by achieving CR early in the treatment course and by sustaining such status for prolonged time durations.

Of interest was the observation that, in the case of relapse from CR, a higher magnitude of M-protein increase in the first 3 months had opposite PRS implications for serum-M (favorable) and urine-M (adverse) levels. Whereas the latter was GEP-risk-independent, higher serum-M levels were associated with superior PRS only in the high-risk setting. We interpret these findings as indicative of urinary light chains being reflective of a less differentiated type of myeloma compared with complete immunoglobulin secretion.

The consistency of data in TT2 and TT3, in the absence and presence of GEP data, provides validation of our CR model. Given its dire prognosis, the high-risk setting requires major emphasis on (1) maximizing the odds of achieving CR status promptly and (2) sustaining such CR for a minimum of 4 to 5 years, beyond which hazard rates decline to levels of low-risk disease.[28] Our results provide a basis for assessing the issue of CR consolidation, especially in high-risk disease, to determine, prospectively, the critical time required for such CR status to be actively sustained.

Acknowledgment

This work was supported by the National Cancer Institute (Program Project Grant CA 55819), Bethesda, MD.

Authorship

Contribution: A.H., J.C., J.D.S., and B.B. designed the study; A.H. and B.B. wrote the manuscript; K.H., Y.A., S.W., B.N., F.v.R., E.A., and B.B. accrued patients and provided clinical care; and A.H., J.C., and J.S. performed statistical analyses.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Table 2. Univariate and multivariate analyses of parameters associated with overall survival

	TT1			TT2			TT3		
Variable	**n/N (%)**	**HR (95% CI)**	***P***	**n/N (%)**	**HR (95% CI)**	***P***	**n/N (%)**	**HR (95% CI)**	***P***
Univariate									
Age ≥ 65 y	21/231 (9)	2.04 (1.29, 3.22)	.002	136/668 (20)	1.44 (1.10, 1.88)	.008	84/303 (28)	1.29 (0.77, 2.16)	.338
Female	88/231 (38)	0.92 (0.68, 1.25)	.592	272/668 (41)	0.83 (0.65, 1.05)	.122	110/303 (36)	1.41 (0.87, 2.28)	.166
White	206/231 (89)	0.98 (0.62, 1.57)	.944	580/668 (87)	1.27 (0.89, 1.83)	.193	268/303 (88)	0.63 (0.33, 1.20)	.156
Albumin < 3.5 g/dL	62/231 (27)	1.09 (0.78, 1.51)	.608	119/664 (18)	1.65 (1.25, 2.17)	<.001	72/303 (24)	1.74 (1.03, 2.92)	.037
B2M ≥ 3.5 mg/L	95/229 (41)	1.55 (1.15, 2.08)	.004	243/668 (36)	1.77 (1.40, 2.23)	<.001	136/303 (45)	2.04 (1.25, 3.32)	.004
B2M > 5.5 mg/L	43/229 (19)	1.69 (1.17, 2.43)	.005	122/668 (18)	2.03 (1.56, 2.65)	<.001	65/303 (21)	3.32 (2.04, 5.39)	<.001
CRP ≥ 8 mg/L	70/223 (31)	1.62 (1.19, 2.22)	.002	263/658 (40)	1.32 (1.04, 1.66)	.021	100/302 (33)	1.66 (1.03, 2.70)	.039
Creatinine ≥ 2 mg/dL	22/231 (10)	1.80 (1.13, 2.87)	.013	62/654 (9)	1.82 (1.29, 2.56)	<.001	23/303 (8)	2.38 (1.21, 4.65)	.012
Hb < 10 g/dL	78/231 (34)	1.53 (1.13, 2.08)	.006	161/667 (24)	1.31 (1.01, 1.69)	.039	94/303 (31)	2.07 (1.28, 3.35)	.003
LDH ≥ 190 U/L	49/230 (21)	1.60 (1.13, 2.27)	.008	204/666 (31)	1.65 (1.30, 2.09)	<.001	81/303 (27)	2.88 (1.78, 4.65)	<.001
CAs	74/221 (33)	1.78 (1.30, 2.43)	<.001	197/661 (30)	2.17 (1.71, 2.74)	<.001	100/302 (33)	3.02 (1.85, 4.91)	<.001
GEP high-risk	NA	NA	NA	46/351 (13)	4.00 (2.70, 5.93)	<.001	40/275 (15)	4.54 (2.69, 7.65)	<.001
GEP CD-1 subgroup	NA	NA	NA	23/351 (7)	0.71 (0.33, 1.52)	.382	15/275 (5)	0.88 (0.27, 2.80)	.822
GEP CD-2 subgroup	NA	NA	NA	45/351 (13)	0.79 (0.45, 1.37)	.400	27/275 (10)	0.65 (0.24, 1.80)	.409
GEP HY subgroup	NA	NA	NA	98/351 (28)	0.59 (0.39, 0.90)	.013	80/275 (29)	0.73 (0.40, 1.33)	.306
GEP LB subgroup	NA	NA	NA	30/351 (9)	0.43 (0.19, 0.98)	.045	33/275 (12)	0.24 (0.06, 0.98)	.046
GEP MF subgroup	NA	NA	NA	19/351 (5)	1.89 (1.02, 3.49)	.044	22/275 (8)	2.58 (1.34, 4.98)	.005
GEP MS subgroup	NA	NA	NA	44/351 (13)	2.08 (1.37, 3.18)	<.001	33/275 (12)	0.77 (0.33, 1.78)	.538
GEP MY subgroup	NA	NA	NA	58/351 (17)	0.98 (0.63, 1.54)	.943	38/275 (14)	0.98 (0.46, 2.06)	.954
GEP PR subgroup	NA	NA	NA	34/351 (10)	2.03 (1.26, 3.26)	.004	27/275 (10)	2.83 (1.50, 5.34)	.001
GEP MF or PR subgroups	NA	NA	NA	53/351 (15)	2.11 (1.41, 3.15)	<.001	49/275 (18)	3.22 (1.91, 5.42)	<.001
GEP MF, MS or PR subgroups	NA	NA	NA	97/351 (28)	2.51 (1.78, 3.53)	<.001	82/275 (30)	2.31 (1.39, 3.84)	.001
GEP HY or LB subgroups	NA	NA	NA	128/351 (36)	0.50 (0.34, 0.73)	<.001	113/275 (41)	0.50 (0.28, 0.89)	.018
GEP MGUS-like	NA	NA	NA	101/351 (29)	0.41 (0.26, 0.65)	<.001	65/275 (24)	0.63 (0.32, 1.24)	.179
Randomized to thalidomide	NA	NA	NA	323/668 (48)	0.79 (0.62, 1.00)	.047	NA	NA	NA
Los-CR*		2.24 (1.61, 3.11)	<.001		4.51 (3.36, 6.06)	<.001		16.28 (7.22, 36.70)	<.001
Did not achieve CR*		1.22 (0.90, 1.65)	.209		1.86 (1.45, 2.38)	<.001		3.24 (1.84, 5.72)	<.001
Multivariate without GEP									
Age ≥ 65 y	20/214 (9)	2.01 (1.24, 3.27)	.005	NS	NS	NS	NS	NS	NS
CAs	74/214 (35)	1.74 (1.25, 2.42)	<.001	188/634 (30)	1.77 (1.39, 2.26)	<.001	100/301 (33)	2.77 (1.69, 4.56)	<.001
B2M > 5.5 mg/L	NS	NS	NS	115/634 (18)	1.54 (1.16, 2.05)	.003	65/301 (22)	2.01 (1.21, 3.33)	.007
CRP ≥ 8 mg/L	70/214 (33)	1.47 (1.06, 2.03)	.021	NS	NS	NS	NS	NS	NS
Creatinine ≥ 2 mg/dL	19/214 (9)	2.23 (1.34, 3.70)	.002	NS	NS	NS	NS	NS	NS
LDH ≥ 190 U/L	NS	NS	NS	197/634 (31)	1.35 (1.04, 1.74)	.025	80/301 (27)	1.88 (1.13, 3.14)	.015
Los-CR*		7.71 (4.09, 14.53)	<.001		8.89 (5.93, 13.33)	<.001		23.01 (8.64, 61.23)	<.001
Did not achieve CR*		3.77 (2.06, 6.90)	<.001		4.03 (2.83, 5.73)	<.001		5.35 (2.69, 10.64)	<.001
Multivariate with GEP									
LDH ≥ 190 U/L	NA	NA	NA	114/334 (34)	1.51 (1.05, 2.16)	.026	74/274 (27)	1.82 (1.06, 3.15)	.031
CAs	NA	NA	NA	108/334 (32)	1.70 (1.19, 2.44)	.004	95/274 (35)	2.83 (1.65, 4.87)	<.001
GEP high-risk	NA	NA	NA	44/334 (13)	2.16 (1.38, 3.38)	<.001	40/274 (15)	2.27 (1.26, 4.09)	.006
GEP HY or LB subgroups	NA	NA	NA	123/334 (37)	0.49 (0.32, 0.76)	.001	NS	NS	NS
GEP MGUS-like	NA	NA	NA	93/334 (28)	0.47 (0.28, 0.74)	.004	NS	NS	NS
Los-CR*	NA	NA	NA		8.66 (4.66, 16.09)	<.001		19.06 (6.88, 52.78)	<.001
Did not achieve CR*	NA	NA	NA		5.60 (3.21, 9.76)	<.001		5.05 (2.50, 10.20)	<.001

The multivariate model uses stepwise selection with entry level 0.1 and variable remains if meets the .05 level. A multivariate *P* value greater than .05 indicates variable forced into model with significant variables chosen using stepwise selection.

HR indicates hazard ratio; CI, confidence interval; *P*, *P* value from Wald χ^2 test in Cox regression; NA, not applicable; and NS, multivariate results not statistically significant at .05 level. All univariate *P* values are reported regardless of significance.

*Treated as a time-dependent variable.

Table 3. Univariate and multivariate analyses of parameters associated with overall survival with combination therapy

	TT1, TT2, and TT3 combined			TT2 and TT3 combined		
Variable	**n/N (%)**	**HR (95% CI)**	***P***	**n/N (%)**	**HR (95% CI)**	***P***
Univariate						
Age ≥ 65 y	241/1202 (20)	1.37 (1.11, 1.68)	.004	220/971 (23)	1.38 (1.08, 1.75)	.009
Female	470/1202 (39)	0.92 (0.77, 1.10)	.357	382/971 (39)	0.93 (0.75, 1.15)	.484
White	1054/1202 (88)	1.08 (0.83, 1.40)	.575	848/971 (87)	1.10 (0.80, 1.50)	.571
Albumin < 3.5 g/dL	253/1198 (21)	1.48 (1.22, 1.80)	<.001	191/967 (20)	1.65 (1.30, 2.10)	<.001
B2M ≥ 3.5 mg/L	474/1200 (40)	1.72 (1.45, 2.03)	<.001	379/971 (39)	1.79 (1.45, 2.21)	<.001
B2M > 5.5 mg/L	230/1200 (19)	2.03 (1.68, 2.47)	<.001	187/971 (19)	2.25 (1.79, 2.83)	<.001
CRP ≥ 8 mg/L	433/1183 (37)	1.40 (1.18, 1.66)	<.001	363/960 (38)	1.39 (1.13, 1.72)	.002
Creatinine ≥ 2 mg/dL	107/1188 (9)	1.86 (1.44, 2.40)	<.001	85/957 (9)	1.92 (1.42, 2.60)	<.001
Hb < 10 g/dL	333/1201 (28)	1.50 (1.25, 1.79)	<.001	255/970 (26)	1.44 (1.15, 1.80)	.001
LDH ≥ 190 U/L	334/1199 (28)	1.71 (1.43, 2.05)	<.001	285/969 (29)	1.85 (1.50, 2.30)	<.001
CAs	371/1184 (31)	2.14 (1.80, 2.55)	<.001	297/963 (31)	2.30 (1.87, 2.84)	<.001
GEP high-risk	NA	NA	NA	86/626 (14)	4.12 (3.02, 5.63)	<.001
GEP CD-1 subgroup	NA	NA	NA	38/626 (6)	0.76 (0.40, 1.44)	.407
GEP CD-2 subgroup	NA	NA	NA	72/626 (12)	0.76 (0.47, 1.24)	.271
GEP HY subgroup	NA	NA	NA	178/626 (28)	0.63 (0.45, 0.89)	.008
GEP LB subgroup	NA	NA	NA	63/626 (10)	0.35 (0.17, 0.72)	.004
GEP MF subgroup	NA	NA	NA	41/626 (7)	2.11 (1.35, 3.29)	.001
GEP MS subgroup	NA	NA	NA	77/626 (12)	1.59 (1.09, 2.31)	.016
GEP MY subgroup	NA	NA	NA	96/626 (15)	0.99 (0.67, 1.45)	.956
GEP PR subgroup	NA	NA	NA	61/626 (10)	2.29 (1.56, 3.34)	<.001
GEP MF, MS, or PR subgroups	NA	NA	NA	179/626 (29)	2.42 (1.83, 3.22)	<.001
GEP HY or LB subgroups	NA	NA	NA	241/626 (38)	0.50 (0.36, 0.68)	<.001
GEP MGUS-like	NA	NA	NA	166/626 (27)	0.48 (0.33, 0.69)	<.001
TT1 protocol	231/1202 (19)	1.54 (1.27, 1.86)	<.001	NA	NA	NA
TT2 protocol	668/1202 (56)	0.83 (0.70, 1.00)	.045	668/971 (69)	1.26 (0.95, 1.66)	.106
TT3 protocol	303/1202 (25)	0.73 (0.56, 0.95)	.020	303/971 (31)	0.80 (0.60, 1.05)	.106
Los-CR*		3.71 (3.00, 4.60)	<.001		5.13 (3.87, 6.79)	<.001
Did not achieve CR*		1.80 (1.50, 2.16)	<.001		2.06 (1.64, 2.59)	<.001
Multivariate without GEP						
CAs	362/1149 (32)	1.85 (1.54, 2.21)	<.001	288/935 (31)	1.93 (1.55, 2.40)	<.001
B2M > 5.5 mg/L	221/1149 (19)	1.63 (1.32, 2.00)	<.001	180/935 (19)	1.63 (1.28, 2.08)	<.001
CRP ≥ 8 mg/L	426/1149 (37)	1.22 (1.02, 1.47)	.032	NS	NS	NS
LDH ≥ 190 U/L	323/1149 (28)	1.35 (1.11, 1.64)	.003	277/935 (30)	1.45 (1.15, 1.82)	.002
Los-CR*		9.26 (6.79, 12.63)	<.001		10.09 (6.95, 14.65)	<.001
Did not achieve CR*		4.45 (3.38, 5.86)	<.001		4.31 (3.15, 5.90)	<.001
Multivariate with GEP						
LDH ≥ 190 U/L	NA	NA	NA	188/608 (31)	1.61 (1.19, 2.18)	<.001
CAs	NA	NA	NA	203/608 (33)	2.13 (1.58, 2.86)	<.001
GEP high-risk	NA	NA	NA	84/608 (14)	1.31 (0.74, 2.30)	<.001
GEP HY or LB subgroups	NA	NA	NA	236/608 (39)	0.53 (0.37, 0.76)	<.001
GEP MGUS-like	NA	NA	NA	157/608 (26)	0.63 (0.41, 0.97)	.034
Los-CR*	NA	NA	NA		10.12 (6.03, 16.99)	<.001
Did not achieve CR*	NA	NA	NA		5.41 (3.52, 8.33)	<.001

The multivariate model uses stepwise selection with entry level 0.1 and variable remains if meets the .05 level. A multivariate *P* value greater than .05 indicates variable forced into model with significant variables chosen using stepwise selection.

HR indicates hazard ratio; CI, confidence interval; *P*, *P* value from Wald χ^2 test in Cox regression; NA, not applicable; and NS, multivariate results not statistically significant at .05 level. All univariate *P* values are reported regardless of significance.

*Treated as a time-dependent variable.

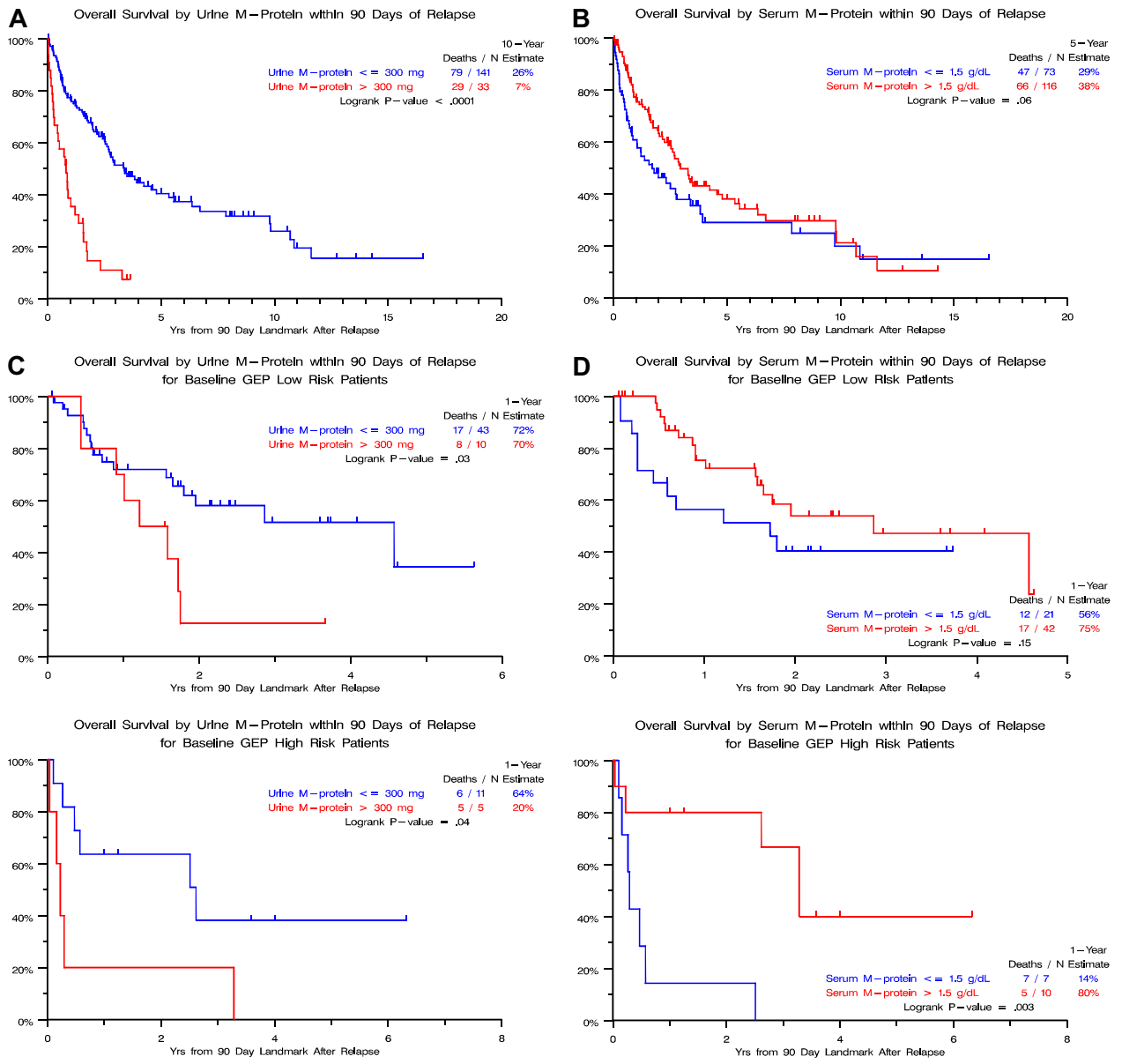

Figure 2. Postrelapse survival by level of urine-M protein or serum M-protein within 90 days of relapse. (A) In the absence of GEP-defined risk designation (TT1, TT2, and TT3 patients combined), postrelapse survival was significantly shorter when urinary M excretion exceeded 300 mg/day than in case of lower values. (B) In the absence of GEP-defined risk designation (TT1, TT2, and TT3 patients combined), postrelapse survival tended to be longer when serum-M levels exceeded 1.5 g/dL than in case of lower levels. (C) In the presence of GEP-defined risk designation, available in subsets of patients treated with TT2 and TT3, postrelapse survival was significantly shorter when urinary M excretion exceeded 300 mg/day than in case of lower values, regardless of GEP-defined risk (low risk, top panel; high risk, bottom panel). (D) In the presence of GEP-defined risk designation, available in subsets of patients treated with TT2 and TT3, postrelapse survival tended to be longer when serum-M levels exceeded 1.5 g/dL than in case of lower levels in the setting of low-risk myeloma (top panel) whereas, in the high-risk setting, postrelapse survival was significantly prolonged (bottom panel).

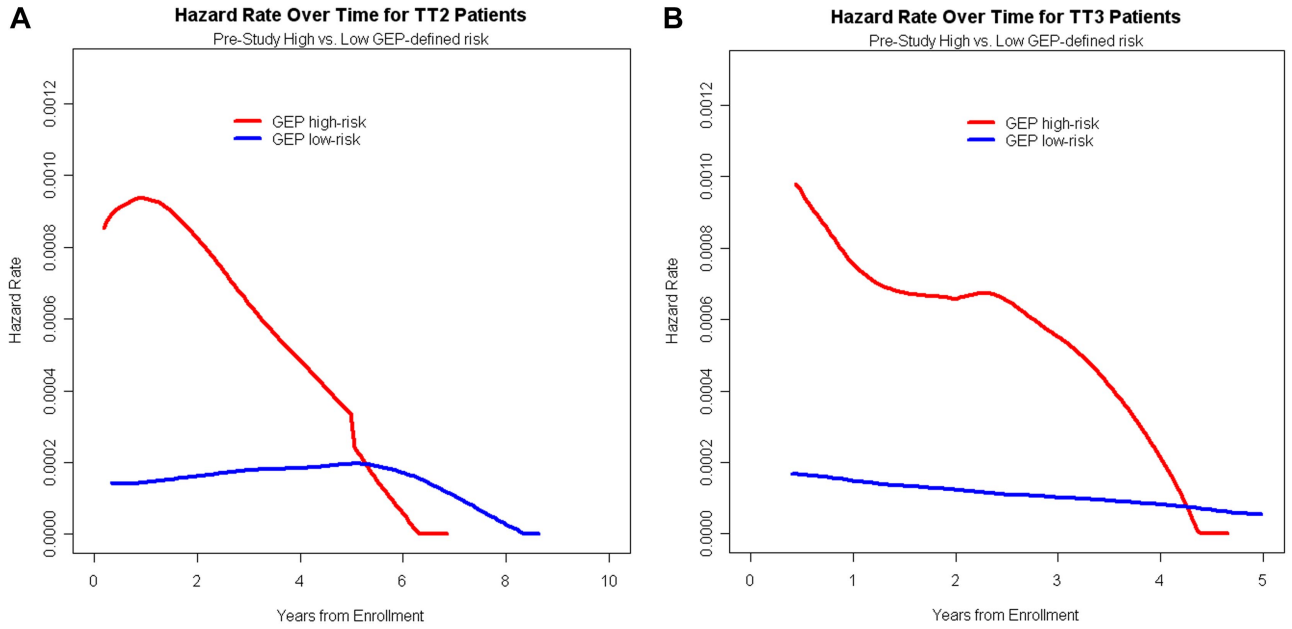

Figure 3. Time-dependent hazard rate of death in TT2 and TT3 protocols according to GEP-defined risk. (A) For TT2, the hazard rate of death declined steeply in high-risk myeloma to reach levels of low-risk disease at 5 to 6 years. (B) For TT3, the hazard rate of death declined steeply in high-risk myeloma to reach levels of low-risk disease at 4 to 5 years.

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