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Early Relapse after Autologous Hematopoietic Cell Transplantation remains a Poor Prognostic Factor in Multiple Myeloma but Outcomes Have Improved Over Time

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CONFLICTS OF INTERESTS

The authors have no conflicts of interests to report.

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Abstract

Duration of initial disease response remains a strong prognostic factor in multiple myeloma (MM) particularly for upfront autologous hematopoietic cell transplant (AHCT) recipients. We hypothesized that new drug classes and combinations employed prior to AHCT as well as after post-AHCT relapse may have changed the natural history of MM in this population. We analyzed the Center for International Blood and Marrow Transplant Research database to track overall survival (OS) of MM patients receiving single AHCT within 12 months after diagnosis (N=3,256) and relapsing early post-AHCT (<24 months), and to identify factors predicting for early vs. late relapses (24–48 months post-AHCT). Over 3 periods (2001–2004, 2005–2008, 2009–2013), patient characteristics were balanced except for lower proportion of Stage III, higher likelihood of 1 induction therapy with novel triplets and higher rates of planned post-AHCT maintenance over time. The proportion of patients relapsing early was stable over time at 35–38%. Factors reducing risk of early relapse included lower stage, chemosensitivity, transplant after 2008 and post-AHCT maintenance. Shorter post-relapse OS was associated with early relapse, IgA MM, Karnofsky <90, stage III, >1 line of induction and lack of maintenance. Post-AHCT early relapse remains a poor prognostic factor, even though outcomes have improved over time.

INTRODUCTION

Autologous hematopoietic cell transplantation (AHCT) continues to be an integral component of initial treatment strategy in eligible patients with multiple myeloma (MM).[1–6] Significant progress has been made in prolonging the duration of initial disease control through judicious combination of effective initial therapy, and AHCT with post-transplant consolidation and maintenance therapy of varying duration.[7, 8] However, most patients eventually relapse and the duration of initial disease control appears to be one of the most important prognostic factors for survival in patients with MM, likely a reflection of the underlying high-risk disease biology that may not be always reflected accurately in the baseline laboratory and MM-relevant fluorescent *in situ* hybridization (FISH) findings.[9–11] Prior studies have shown that the time to progression after AHCT reliably predicts the overall survival from the time of relapse and in fact this has been commonly used as a metric for determining the potential benefit from a second AHCT used as salvage therapy.[9, 12, 13] In a study of 432 patients transplanted at Mayo Clinic within 12 months of their diagnosis, 94 patients (22%) had relapsed within 12 months of their transplant.[12] Median overall survival (OS) from diagnosis was 23.9 months in the early relapse group compared to 82.2 months in

the late relapse group. Among the 265 patients who had disease progression after transplant, median overall survival from relapse was only 7.8 months for the early relapse group compared to 39.6 months for the late relapse group. Most of the available data reflect prior treatment approaches and the improvements in therapy over the past decade including the use of new drug classes and routine incorporation of post AHCT maintenance is likely to have altered these estimates. Finally, the risk factors associated with early treatment failure following AHCT as well as those associated with inferior outcomes post-relapse are not well understood in the context of modern therapies, and this knowledge will allow us to better predict risk and design clinical trials to improve outcomes.

We undertook the current study to specifically address how these clinical scenarios and their implications have changed during the recent decade, given the dramatic change in treatments and consequent improvement in OS of patients with MM. Specifically, we wanted to determine if risk of early relapse after AHCT has changed, if OS after early relapse has improved, the factors predicting early and late relapses after AHCT, and to compare post-relapse survival among patients suffering an early relapse (<24 months from transplant) and those with more durable disease control. We used the Center for International Blood and Marrow Transplant Research (CIBMTR) database to conduct this analysis.

PATIENTS AND METHODS

Data Source

The CIBMTR is a prospectively maintained transplant database that captures transplant data from over 500 transplant centers worldwide. Data are submitted to a statistical center at the Medical College of Wisconsin in Milwaukee. Participating centers are required to report all transplants consecutively; patients are followed longitudinally and compliance is monitored by onsite audits. Computerized checks for discrepancies, physicians' review of submitted data, and onsite audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

The specific objectives for the study were to determine if OS has improved between January 2001 and December 2013 among patients relapsing early (<24 months) after an AHCT, to determine factors predicting early and late relapses (24–48 months) after AHCT and to compare post-relapse survival among early relapse (<24 months from AHCT) and late relapse (24–48 months from AHCT).

Patient Selection

Patients who underwent first AHCT for MM in the United States or Canada from 2001–2013 and reported to CIBMTR were considered for the current study. Patients undergoing late AHCT (>12 months from diagnosis), those undergoing tandem transplants, those receiving non-melphalan based conditioning, and those with unknown induction treatment agents were excluded. Patients were required to have at least 100 days follow up or death

prior to 100 days after AHCT and should have consented to research participation; those with unknown relapse status were excluded. The disposition of patients who were considered for inclusion is detailed in supplementary table 1.

Endpoints

The endpoints of interest included disease response, progression-free survival (PFS), and OS after transplant. Disease response was assessed using the International Myeloma Working Group (IMWG) consensus criteria.[14] PFS was defined as time without progressive disease with patients alive and without progression/relapse censored at last follow-up. OS was defined as time from diagnosis or time of relapse after AHCT till death from any cause with censoring of surviving patients at last follow-up.

Statistical Methods

We examined the post-transplant OS in the entire cohort from diagnosis of myeloma, and OS from post-AHCT relapse in the group of patients with a documented relapse occurring within 24 months of AHCT comparing it to those with a relapse after 24 months or none at the time of last follow up. Univariate analysis was conducted to compare post-AHCT OS among the early relapse group over time. Patients were divided in 3 groups based on year of transplant, 2001–2004, 2005–2008 and 2009–2013. Two separate multivariate analyses were conducted: 1) Time to relapse from transplant was analyzed to identify factors associated with early relapse and relapse after 24 months. We fitted a left-truncation model where patients who relapsed after 24 months, their relapse time was truncated at 24 months. Factors that were studied included age, gender, race, Karnofsky Performance Score (KPS) at transplant, MM subtype (IgG, IgA, light chain, non-secretory, others), serum creatinine at diagnosis, stage at diagnosis (International Staging System or Durie Salmon Stage III versus I/II), lines of pre-transplant chemotherapy, novel triplet versus novel doublet versus non-novel induction, melphalan conditioning dose, chemosensitivity, disease status at transplant, time from diagnosis to transplant, year of transplant, planned post-transplant therapy; 2) Post-relapse OS- this analysis which was conducted on all relapsed patients and included early versus late relapse in addition to all the aforementioned characteristics in the multivariate model.

RESULTS

The study included 3256 patients who underwent AHCT within 12 months of diagnosis and had data reported to the CIBMTR. The baseline characteristics are as shown in Table 1. The study cohort was divided into three groups based on the year of AHCT: 2001–2004 (n=896), 2005–2008 (n=1401) and 2009–2013 (n=959). Patients in the most recent group were more likely to have received induction therapy with bortezomib, lenalidomide and dexamethasone, compared to the previous years and were more likely to come to transplant with a single line of prior therapy, reflecting the improved efficacy of current regimens. A higher proportion of patients received their transplant within 6 months from diagnosis in the most recent cohort. The median follow up from AHCT of the survivors in the three groups were 120, 86 and 39 months respectively.

Time of relapse and post-transplant outcomes

At the time of analysis, 17%, 20% and 46% of patients were alive without disease progression in the 2001–2004, 2005–2008, and 2009–2013 groups, respectively (Table 2). A higher proportion of patients in the most recent period had intent for planned post-AHCT consolidation and/or maintenance (72%) compared with 23% for the middle group and 6% for the earliest group. Median follow-up of survivors was 120 (3–170) months for 2001–2004, 86 (3–129) months for 2005–2008 and 39 (3–82) months for 2009–2013 groups. The median PFS from AHCT for the 2001–2004, 2005–2008, and 2009 to 2013 groups was 31.2, 29.9 and 30.4 months, respectively (Figure 1A). The median OS for the three groups were 65.5, 79.5 and 88.8 months ($p<0.001$), respectively, suggesting improving survival over the time period. (Figure 1B) A similar proportion of patients had relapsed within 12 and 24 months of AHCT during the three time periods (Table 2). Overall, 38%, 38% and 35% of patients had relapsed within 24 months of AHCT in the three groups respectively (Figure 1C).

We initially examined the impact of early post-AHCT relapse on OS of patients and how it has changed in the recent years. The OS from diagnosis was 44.7 months (95% CI: 42.5–48.2) for those relapsing within 24 months of AHCT compared with 113.7 months (95% CI: 108.2–121.7) for those who had not relapsed within 24 months, reflecting the poor disease biology associated with early relapse (Figure 2A). Among those relapsing within 24 months, the median OS from diagnosis was 38.1, 48.1 and 48.3 for 2001–2004, 2005–2008, and 2009–2013 groups, respectively. For the remaining patients, the median OS from diagnosis was 102, 115.5 and 97.8 for the three time periods, respectively (p-value NS).

Post-relapse outcomes

We evaluated the survival outcomes from relapse, comparing the outcomes of those relapsing within 24 months of AHCT and those relapsing beyond 24 months from AHCT or have not relapsed at last follow up. The baseline characteristics and the transplant related characteristics of these three groups of patients are as shown in Table 3. On multivariate, factors influencing early relapse included advanced MM stage [Hazard Ratio, (HR) 1.2; 95%CI: 1.0–1.3; p=0.02], chemo sensitivity (HR 0.8; 95%CI: 0.7–0.9, p=0.007), transplant after 2008 (HR 0.8; 95%CI: 0.7–0.98; p=0.02), and post-AHCT maintenance with novel agent (HR 0.8; 95%CI: 0.7–1.0, p=0.02) (Table 4).

The median OS from the time of relapse was significantly inferior for the early relapse group compared with the late relapse groups; $P<0.001$ (Figure 2B, Table 5a). Next, we observed that while post-relapse survival of both early and late relapse were improved in the 2005–2013 period compared to 2001–2004, but improvements seemed greater for the late relapse group than for the early relapse group by year of transplant (Figure 2C). We then specifically examined the survival trends among the early relapse patients. Compared to patients transplanted in 2001–2004, patients with early relapse in the two later groups had improved OS from relapse (Figure 2D). The survival estimates over time for this group of patients are shown in Table 5b. We also examined the OS from relapse based on disease relapse before or after 2005. The median OS from relapse for those relapsing before 2005

was 16.4 months compared with 24.7 months for those relapsing after 2005; P <0.001. The survival estimates over time for this group of patients are shown in Table 5c.

We subsequently performed multivariate analysis to examine factors predicting for post-relapse OS among patients relapsing early or late after AHCT. Risk factors for post-relapse OS on multivariate analysis included early relapse (HR 1.4; 95%CI: 1.3–1.6, p<0.0001), Karnofsky <90 (HR 1.2; 95%CI: 1.1–1.4; p=0.007), stage III myeloma (HR 1.3; 95%CI: 1.1–1.4, p<0.0001), 2+ lines of chemotherapy (HR 1.2; 95%CI: 1.1–1.4, p=0.005), novel agent maintenance post-AHCT (HR 0.7; 95%CI: 0.6–0.9, p<0.0001), and IgA myeloma (HR 1.3; 95%CI: 1.1–1.5; p=0.0006) (Table 6).

DISCUSSION

As the outcomes for MM patients continue to improve, disease heterogeneity has become increasingly evident, with nearly a quarter of patients continuing to have median overall survival of 2–3 years.[15–20] These ‘high-risk’ patients are typically characterized by the presence of one or more cytogenetic abnormalities, but these abnormalities do not always account for the poor outcomes seen in some patients. Over the years, it has become apparent that patients with a short duration of response, particularly those relapsing early after AHCT, have a poor outcome, defining a functional high risk group of patients.[9, 10, 12] Even in the current era with major improvements in the treatment approaches, especially more uniform application of highly effective regimens incorporating proteasome inhibitors and immunomodulatory drugs, AHCT continues to play a major role in the treatment of myeloma.[2, 6, 7, 21] It is considered a standard component of the initial treatment approach for patients who can undergo this procedure. Much has changed in the context of transplant with better induction therapy, and uniform incorporation of post-transplant approaches such as consolidation and maintenance.[4, 22–29] This study was undertaken to examine the clinical factors predicting early relapse in the face of these improvements in initial therapy and if the post relapse outcomes have improved with the increasing availability of novel classes of agents.

Examination of the baseline characteristics of the patients included in this study gives valuable information regarding the changing landscape of transplant utilization in North America, in the context of which the current results should be interpreted.[2] The demographic characteristics of the patients going to transplant within 12 months of diagnosis has remained consistent over the study period. It is interesting to note a trend towards decreasing proportion of patients with International Staging System (ISS) stage 3 in the recent years, and may reflect an overall shift towards earlier treatment intervention among patients, a fact to be considered when interpreting the results.[8] The type of induction regimens utilized pre-AHCT shows a significant shift towards use of proteasome inhibitor/immunomodulatory drug combinations such as VRD, which was used in nearly half of the patients in the recent group. The increased use of this regimen is consistent with the current recommendations based on results from the phase 3 trial of this regimen.[30, 31] The impact of this shift in induction regimen likely explains the increasing proportion of patients coming into transplant with just one line of initial therapy in the most recent cohort, and with chemo sensitive disease. The quicker response seen with the newer regimens also likely explains the

higher proportion of patients receiving transplant within 6 months of diagnosis in the most recent group. Finally, as expected a significantly higher proportion of patients were reported to have planned post-AHCT therapy in the form of maintenance with lenalidomide or bortezomib.

One of the striking findings of the current study is the lack of a substantial decrease in the proportion of patients who are relapsing within 24 months after AHCT; 38%, 38% and 35% during the three consecutive periods. Given that patients are likely to be going into transplant with more chemo sensitive disease, likely a deeper response and higher proportion with planned post AHCT therapy, the lack of improvement in this aspect of disease is intriguing as well as concerning. One potential explanation is that patients with genetically high-risk disease are being preferentially being steered towards transplant, but the proportion of ISS stage 3 disease being less in the recent years makes this explanation less likely. The proportion of patients progressing within 24 months of the transplant in the latest group is consistent with the findings from the phase 3 trial.[28, 29] In the CALGB 100104 trial nearly 50% and 25% of patients in the observation and maintenance lenalidomide arms, respectively had relapsed within 24 months consistent with the 36% overall rate of progression seen here.[29] It is possible that more patients whose disease achieve less than a VGPR after AHCT in the earlier years may have gone on to tandem AHCT and thus would be excluded from the current study.[32] It is also possible this represents underlying biology, that is not being significant impacted by the alterations in the short course of induction therapy regimen or the post AHCT maintenance, but rather reflect an innate resistance to high-dose therapy. This is further underscored by the fact that the induction regimens were similar among the patients with a relapse within 24 months and those relapsing after 24 months. If that is indeed the case, it is important to understand the drivers and possibly predict the suboptimal outcomes such that we can design clinical trials for this high-risk patient population. The analysis does shed some light into the predictors of early relapse, information that could be utilized in designing clinical trials for this patient group.

Consistent with prior data, patients with early relapse continues to represent a poor prognosis subgroup of patients, who clearly need a different approach to their management. [9, 12] In the current study, those relapsing within 24 months of transplant had a significantly shorter OS from the time of relapse, compared to those relapsing 24–48 months from AHCT. However, it is encouraging to see the improvement in survival of patients from the time of relapse in this high-risk group of patients over the years. The improvement is evident starting somewhere in the 2004–2008 period, and seems to be maintained over the subsequent years (Figure 2D). This improvement in post-relapse survival likely reflects the introduction of the newer drugs and more consistent availability of these drugs and the use of drug combinations in the setting of relapsed disease. However, the lack of further improvement between the 2005–08 cohort and the most recent group highlights the need for continued development of novel strategies. It is likely the effect of more recent improvements seen with newer drugs such as carfilzomib (FDA-approved in mid-2012), pomalidomide (FDA-approved in early 2013), ixazomib and monoclonal antibodies (FDA-approved later 2015) is likely not reflected here as our dataset covers practice in 2000–2013. In addition to the timing of relapse, several other risk factors for poor outcome following post AHCT relapse have been identified in the multivariate analysis. These include

previously described factors such as the older age and poorer performance status, ISS stage III at diagnosis, IgA myeloma and >1 line of therapy prior to AHCT as well as lack of maintenance therapy following AHCT. It is certainly of interest that the post-relapse survival is higher among those who relapse on maintenance, suggesting lack of development of a more resistant disease phenotype among maintained patients and the availability of new classes of drugs in the recent years. This finding is consistent with what was seen in a recent meta-analysis of trials using post AHCT maintenance.[33]

The major limitation of our study is the lack of cytogenetic data on patients. Because the CIBMTR only collected cytogenetic data after 2008, it is not possible to obtain this information. Further, even in the 2008–2013 cohort, there may be heterogeneous FISH methodology, variable plasma cell enrichment, and possibility of false negative results. Patients defined as stage 3 include DSS and/or ISS 3 given that the ISS was only developed in 2004 and our data includes patients from the pre-ISS era. Lastly, we are unable to characterize whether the reported relapses were biochemical, clinical or radiological. Nevertheless, this study allows us, using a large database capturing the majority of MM AHCT activity in the region, to study systematically early relapsers after AHCT and assess changes in outcomes over time.

In conclusion, early relapse after initial therapy, in the context of an upfront transplant in this study, continues to be a risk and biology defining feature in myeloma. A relatively high constant proportion of patients with early relapse highlights critical aspects of biology that are not being addressed by current prognostic factors at diagnosis or current therapies. Identification of risk factors and well-designed laboratory studies of the tumor and microenvironment in these patients will lead to further improvements over time. The improved outcomes from relapse is encouraging and this is likely to improve over time with introduction of newer therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

DISCLOSURES

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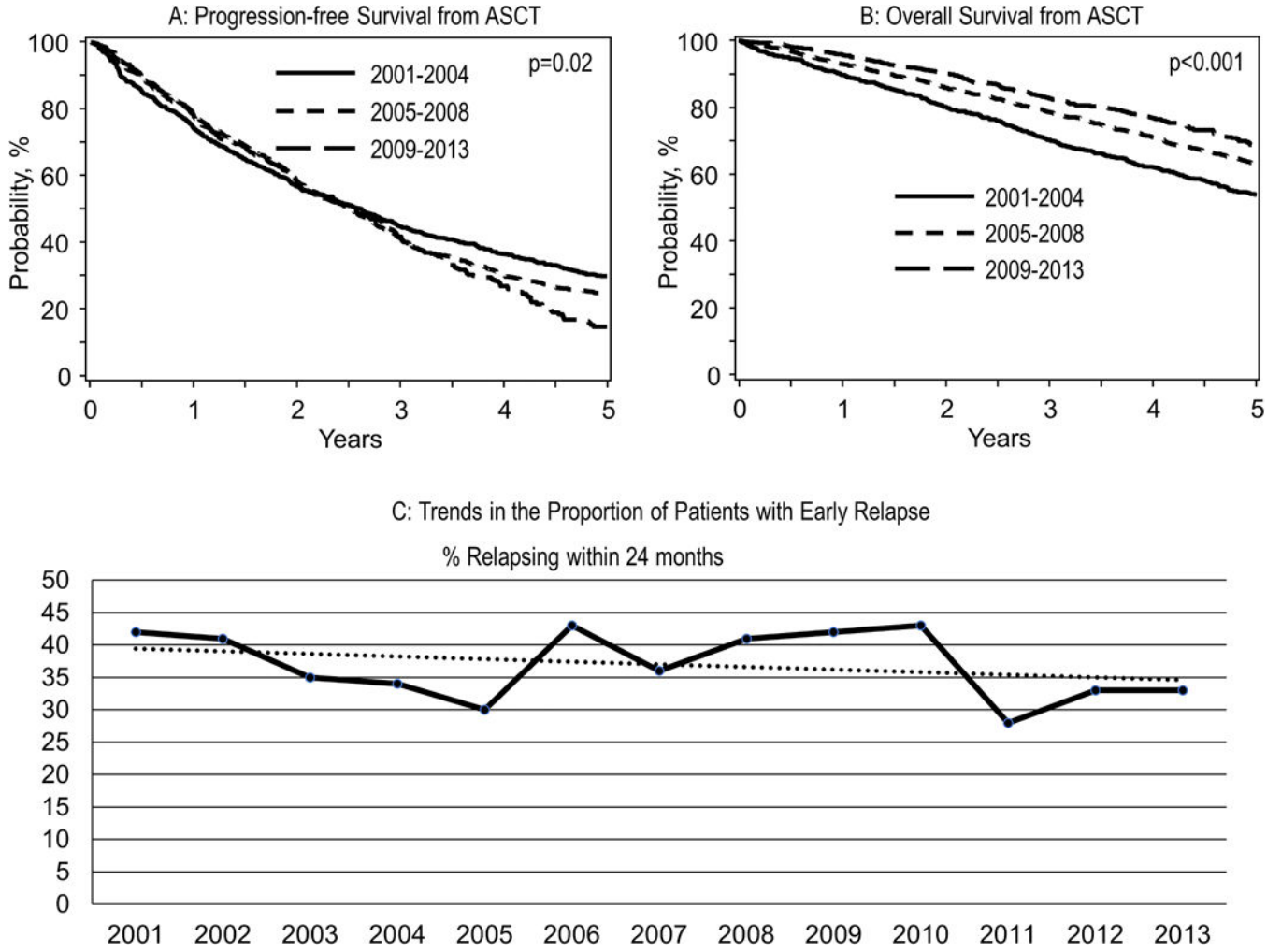

Figure 1.

Panel A: Progression free survival from AHCT for the three groups of patients by the date of AHCT (2001-204, 2005–2008, 2009–2013).

Panel B: Overall survival from AHCT for the three groups of patients by the date of AHCT (2001-204, 2005–2008, 2009–2013)

Panel C: Trends in the proportion of patients with early relapse

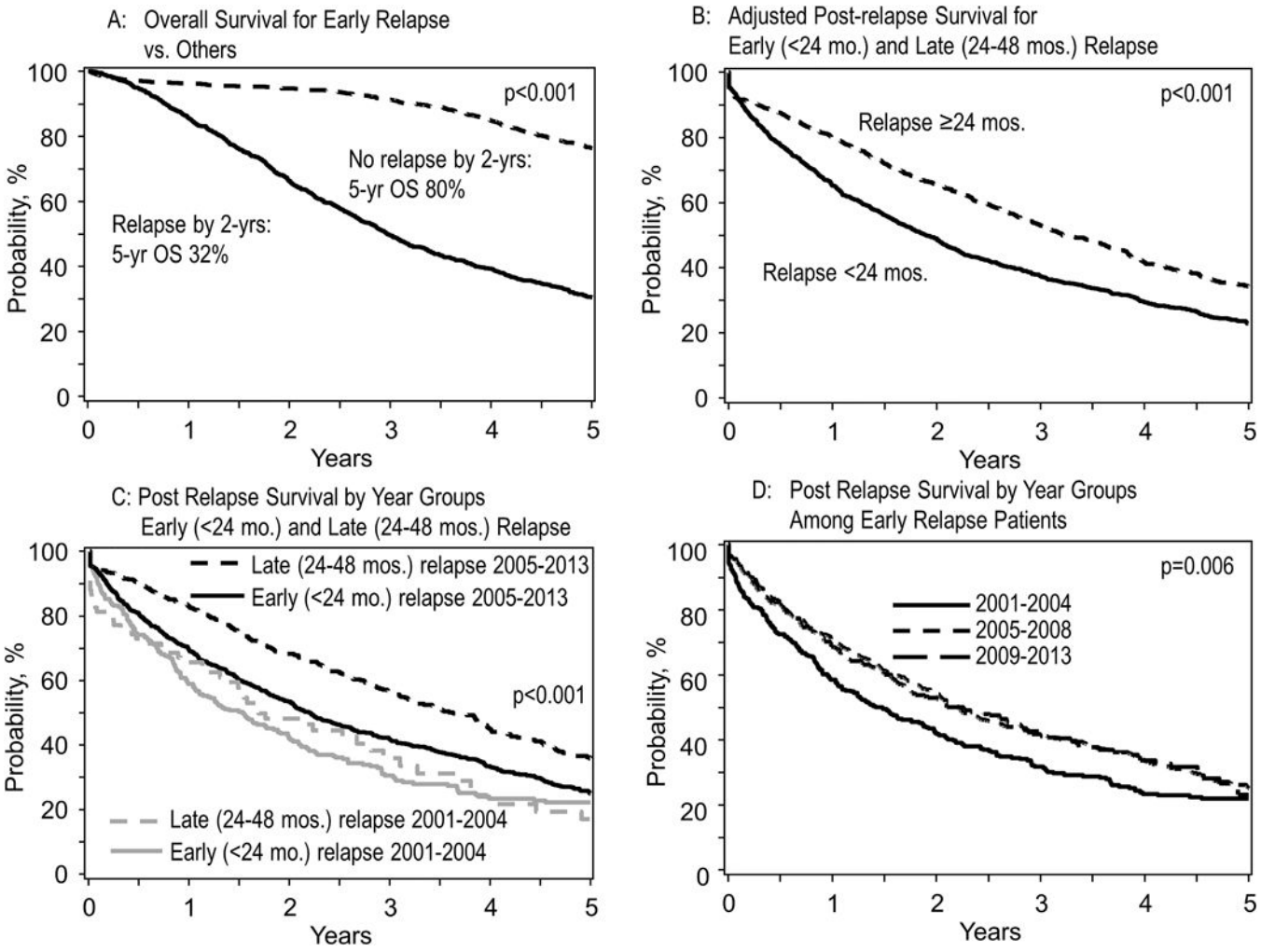

Figure 2.

Panel A: Overall survival from diagnosis among patients with early relapse (< 24 months) and late relapse (>24 months)

Panel B: Post-relapse survival for early relapse patients (relapse within 24 months) compared to those with a late relapse

Panel C: Post-relapse survival for early relapse patients who relapsed within 24 months grouped by relapse year 2005

Panel D: Post-relapse survival for early relapse patients who relapsed within 24 months, grouped by the date of AHCT (2001-204, 2005–2008, 2009–2013)

Table 1

Patient characteristics at diagnosis

Variable	2001–2004	2005–2008	2009–2013
Number of patients	896	1401	959
Number of centers	102	99	99
Age at transplant, years			
median age (range)	59 (22–80)	59 (23–80)	59 (28–78)
Gender			
Male	536 (60)	841 (60)	558 (58)
Region			
US	761 (85)	1319 (94)	950 (99)
Canada	135 (15)	82 (6)	9 (<1)
Karnofsky Score			
≥ 90%	533 (59)	736 (53)	519 (54)
< 90%	316 (35)	501 (36)	390 (41)
Unknown	47 (5)	164 (12)	50 (5)
Disease-related variables			
Immunochemical subtype			
IgG	517 (58)	762 (54)	551 (57)
IgA	190 (21)	313 (22)	196 (20)
Light chain	147 (16)	267 (19)	183 (19)
Others	9 (1)	17 (1)	15 (2)
Non-secretory	28 (3)	40 (3)	14 (1)
Unknown Type	5 (<1)	2 (<1)	0
Serum creatinine at diagnosis			
< 2 mg/dl	595 (66)	930 (66)	664 (69)
≥ 2 mg/dl	135 (15)	235 (17)	147 (15)
Unknown	166 (19)	236 (17)	148 (15)
Serum albumin at diagnosis			
< 3.5 g/dl	274 (31)	416 (30)	313 (33)
≥ 3.5 g/dl	388 (43)	676 (48)	486 (51)
Unknown	234 (26)	309 (22)	160 (17)
ISS/DSS Stage III			
Yes	389 (43)	538 (38)	292 (30)
No	487 (54)	803 (57)	588 (61)
Missing	20 (2)	60 (4)	79 (8)
Transplant-related variables			
Lines of chemotherapy			
1	606 (68)	956 (68)	779 (81)
2	236 (26)	358 (26)	140 (15)
3+	54 (6)	87 (6)	40 (4)
Chemotherapy			

Variable	2001–2004	2005–2008	2009–2013
VTD	9 (1)	189 (13)	62 (6)
RVD	0	79 (6)	467 (49)
CVD	3 (<1)	117 (8)	134 (14)
VD	3 (<1)	86 (6)	145 (15)
RD	2 (<1)	216 (15)	124 (13)
TD	184 (21)	485 (35)	15 (2)
VAD/similar	695 (78)	229 (16)	12 (1)
Melphalan dose (mg/m^2) for condition regimen			
140	167 (19)	230 (16)	100 (10)
200	729 (81)	1171 (84)	859 (90)
Total No. of CD34 cells infused (×10^6/kg)			
Median (range)	6 (1–20)	5 (1–20)	4 (2–19)
Disease status at transplant			
CR	139 (16)	177 (13)	168 (18)
VGPR[†]	(NA)	(NA)	330 (34)
PR	635 (71)	1069 (76)	408 (43)
MR/NR/SD	98 (11)	113 (8)	36 (4)
Relapse/Progression	21 (2)	42 (3)	17 (2)
Unknown	3 (<1)	0	0
Sensitivity to chemotherapy			
Sensitive	774 (86)	1246 (89)	906 (94)
Resistant	119 (13)	155 (11)	53 (6)
Unknown	3 (<1)	0	0
Time from diagnosis to transplant			
< 6 months	284 (32)	391 (28)	399 (42)
6 – 12 months	612 (68)	1010 (72)	560 (58)
Median follow-up of survivors (range), months	120 (3–170)	86 (3–129)	39 (3–82)

Legend: ISS, International Staging System; DSS, Durie Salmon Stage, VTD, boretezomib, thalidomide and dexamethasone; RVD, lenalidomide, bortezomib and dexamethasone; CVD, cyclophosphamide, bortezomib and dexamethasone; VD, bortezomib, dexamethasone; RD, lenalidomide, dexamethasone; TD, thalidomide, dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; NR, no response; SD, stable disease.

[†]This was included only after 2008. Prior to 2008, VGPR patients would be included in PR group

Table 2

Post-transplant characteristics

Variable	2001–2004	2005–2008	2009–2013
Post-relapse salvage transplant			
No salvage transplant	702 (78)	1097 (78)	890 (93)
Salvage Auto transplant	165 (18)	254 (18)	58 (6)
Salvage Allo transplant	29 (3)	50 (4)	11 (1)
Time from transplant to relapse			
NRM	74 (8)	83 (6)	23 (2)
< 12 months	155 (17)	280 (20)	444 (46)
12 – 24 months	201 (22)	265 (19)	198 (21)
24 – 36 months	141 (16)	270 (19)	138 (14)
36 – 48 months	94 (10)	218 (16)	80 (8)
>= 48 months	62 (7)	133 (9)	41 (4)
No relapse and alive	169 (19)	152 (11)	35 (4)
Planned post-HCT therapy			
Novel agents (Lena+Bort/Lena/Bort)‡	30 (3)	267 (19)	695 (72)
Other agents	29 (3)	54 (4)	6 (<1)
None	818 (91)	1010 (72)	236 (25)
Missing	19 (2)	70 (5)	22 (2)

Legend NRM: non-relapse mortality

Table 3

Characteristics of patients grouped by timing of relapse*

Variable	Relapse <24 months	Relapse after 24 months	No Relapse
Number of patients	1156	984	893
Age at transplant, years			
median age (range)	58 (31–80)	60 (28–78)	59 (22–80)
<50	216 (19)	171 (18)	167 (19)
50–69	857 (75)	747 (76)	676 (76)
70+	83 (7)	66 (7)	50 (6)
Gender			
Male	697 (60)	596 (61)	512 (57)
Karnofsky Performance Score			
≥ 90%	623 (54)	535 (54)	506 (57)
< 90%	436 (38)	369 (38)	331 (37)
Unknown	97 (8)	80 (8)	56 (6)
Disease-related variables			
Immunochemical subtype			
IgG	619 (54)	565 (57)	519 (58)
IgA	300 (26)	209 (21)	152 (17)
Light chain	186 (16)	169 (17)	191 (21)
Others	17 (1)	12 (1)	9 (1)
Non-secretory	31 (3)	27 (3)	20 (2)
Serum Creatinine at diagnosis			
< 2 mg/dl	787 (68)	666 (68)	597 (67)
≥ 2 mg/dl	196 (17)	152 (15)	131 (15)
Unknown	173 (15)	166 (17)	165 (18)
Serum Albumin at diagnosis			
< 3.5 g/dl	384 (33)	306 (31)	254 (28)
≥ 3.5 g/dl	515 (45)	473 (48)	448 (50)
Unknown	257 (22)	205 (21)	191 (21)
ISS/DS Stage III			
Yes	474 (41)	367 (37)	300 (34)
No	629 (54)	580 (59)	554 (62)
Missing	53 (5)	37 (4)	39 (4)
Transplant-related variables			
Lines of chemotherapy			
1	783 (68)	701 (71)	683 (76)
2	302 (26)	223 (23)	167 (19)
3+	71 (6)	60 (6)	43 (5)

Variable	Relapse <24 months	Relapse after 24 months	No Relapse
Chemotherapy			
VTD	98 (8)	93 (9)	64 (7)
RVD	181 (16)	94 (10)	211 (24)
CVD	80 (7)	63 (6)	72 (8)
VD	76 (7)	55 (6)	79 (9)
RD	134 (12)	88 (9)	103 (12)
TD	234 (20)	276 (28)	152 (17)
VAD/similar	353 (31)	315 (32)	212 (24)
Melphalan dose (mg/m^2) for condition regimen			
140	198 (17)	146 (15)	128 (14)
200	958 (83)	838 (85)	765 (86)
Total No. of CD34 cells infused (×10^6/kg)			
Median (range)	4.81 (1.00–19.11)	5.34 (1.18–19.70)	5.08 (1.19–19.56)
Disease status at transplant			
CR	142 (12)	140 (14)	171 (19)
PR	860 (74)	760 (77)	652 (73)
MR/NR/SD	108 (9)	67 (7)	56 (6)
Relapse/Progression	45 (4)	16 (2)	14 (2)
Unknown	1 (<1)	1 (<1)	0
Sensitivity to chemotherapy			
Sensitive	1002 (87)	900 (91)	823 (92)
Resistant	153 (13)	83 (8)	70 (8)
Unknown	1 (<1)	1 (<1)	0
Time from diagnosis to transplant			
< 6 months	368 (32)	325 (33)	301 (34)
6 – 12 months	788 (68)	659 (67)	592 (66)
Year of transplant			
2001–2004	331 (29)	325 (33)	198 (22)
2005–2008	520 (45)	503 (51)	323 (36)
2009–2013	305 (26)	156 (16)	372 (42)
Median follow-up of survivors (range), months	75 (24–169)	97 (25–170)	60 (24–170)
Post-transplant characteristics			
Post-relapse salvage transplant			
No salvage transplant	938 (81)	699 (71)	893
Salvage AutoHCT	159 (14)	267 (27)	0
Salvage AlloHCT	59 (5)	18 (2)	0
Time from transplant to relapse			
< 12 months	624 (54)	0	
12 – 24 months	532 (46)	0	

Variable	Relapse <24 months	Relapse after 24 months	No Relapse
24 – 36 months	0	392 (40)	
> 36 months	0	236 (24)	
Planned post-HCT therapy			
Novel agents (Lena+Bort/Lena/Bort)	272 (24)	254 (26)	370 (41)
Other agents	20 (2)	39 (4)	28 (3)
None	813 (70)	644 (65)	485 (54)
Missing	51 (4)	47 (5)	10 (1)

* Limited to patients with at least 24 months follow up if still alive

Legend VTD, boretezomib, thalidomide and dexamethasone; RVD, lenalidomide, bortezomib and dexamethasone; CVD, cyclophosphamide, bortezomib and dexamethasone; VD, bortezomib, dexamethasone; RD, lenalidomide, dexamethasone; TD, thalidomide, dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; NR, no response; SD, stable disease; HCT hematopoietic cell transplantation

Table 4

Risk factors of early relapse (within 24 months)*

Variable		Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
Sensitivity to chemotherapy	Overall				0.0071
	Resistant	1.000			
	Sensitive	0.824	0.715	0.949	0.0071
Year of transplant	Overall				0.0179
	2001–2008	1.000			
	2009–2013	0.839	0.720	0.978	0.0179
ISS/DS Stage III At Diagnosis	Overall				0.0132
	No	1.000			
	Yes	1.152	1.047	1.268	0.0037
Post-transplant maintenance	Overall				0.0247
	No/Other agent	1.000			
	Novel agent	0.813	0.692	0.957	0.0180
Year of transplant # Post transplant maintenance	Overall				0.0003
	2001–2008, No/Other vs. Novel Agents	1.219	1.035	1.436	<.0001
	2009–2013, No/Other vs. Novel Agents	1.256	1.025	1.538	<.0001

*All patients were included in the analysis, including patients who didn't relapse

#Risk factors are the same for either early or late relapse

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Table 5

a. Post-relapse survival based on timing of relapse (early vs. late)

	Relapse within 24 months (N = 1156)		Relapse after 24 months (N=984)		
Outcomes	**Number**	**Probability (95% CI)**	**Number**	**Probability (95% CI)**	**p-value**
Post relapse survival	1155		984		<0.001
1-year		65 (63–68)%		80 (77–82)%	
2-year		50 (47–53)%		66 (62–69)%	
3-year		38 (35–41)%		53 (49–56)%	
4-year		30 (27–33)%		41 (38–45)%	

b. Post-relapse survival trend of early relapse within 24 months during transplant year from 2001–2013

	2001–2004 (N = 342)		2005–2008 (N = 535)		2009–2013 (N = 336)		
Outcomes	**Number**	**Probability (95% CI)**	**Number**	**Probability (95% CI)**	**Number**	**Probability (95% CI)**	**p-value**
Overall Survival	342		535		336		0.006
1-year		58 (53–64)%		70 (66–74)%		68 (63–73)%	
2-year		42 (37–47)%		54 (50–59)%		53 (47–59)%	
3-year		32 (27–37)%		42 (37–46)%		41 (35–47)%	
5-year		22 (17–27)%		25 (21–29)%		23 (16–31)%	

c. Post-relapse survival of early relapse within 24 months by relapse year before and after 2005

	Relapsed before 2005 (N = 284)		Relapsed in or after 2005 (N = 929)		
Outcomes	**Number**	**Probability (95% CI)**	**Number**	**Probability (95% CI)**	**p-value**
Post relapse Survival	284		929		0.005
1-year		59 (53–64)%		69 (66–72)%	
2-year		42 (36–48)%		53 (50–57)%	
3-year		30 (25–36)%		41 (38–45)%	
4-year		23 (18–29)%		33 (29–36)%	
5-year		22 (17–27)%		25 (21–28)%	

Table 6

Multivariate analysis of post-relapse survival

Variable	Number	Hazard Ratio	95% Confidence Interval	p-value
Relapse Group				<0.0001
-Late relapse	628	1		
-Early relapse	1213	1.43	1.26, 1.62	
Age at AHCT				0.06
-18–49	334	1		
-50–59	648	1.15	0.97, 1.37	0.10
-60–69	727	1.23	1.04, 1.46	0.02
-70+	132	1.33	1.03, 1.71	0.03
Stage III at Diagnosis				<0.0001
-No	1010	1		
-Yes	747	1.28	1.13, 1.45	<0.0001
-Missing	84	1.01	0.73, 1.40	0.89
Immunochemical subtype				0.0006
-IgG	1010	1		
-IgA	441	1.30	1.13, 1.49	0.0002
-Light chain	309	0.90	0.76, 1.06	0.20
-Non-secretory/others	73	1.00	0.74, 1.35	1.00
-Missing	4	0.83	0.27, 2.61	0.75
Karnofsky Performance Score at AHCT				0.007
-≥90%	995	1		
-<90%	686	1.21	1.07, 1.36	0.003
-Missing	160	1.07	0.86, 1.34	0.82
Lines of Pre-AHCT chemotherapy				0.005
-1	1273	1		
-2+	568	1.20	1.10, 1.35	
Post-transplant maintenance				<0.0001
-No/Other agents	1286	1		
-Novel agents	473	0.73	0.63, 0.85	<0.0001
-Missing	82	0.60	0.45, 0.80	0.0006

Legend AHCT, autologous hematopoietic cell transplantation