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BRIEF COMMUNICATION

Upfront tandem autologous non-myeloablative allogeneic stem cell transplant in high-risk multiple myeloma: a long-term single-centre experience

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Abstract

The role of upfront non-myeloablative allogeneic stem cell transplantation (NMA alloSCT) in high-risk multiple myeloma (HR-MM) is unclear. We evaluated outcomes of NMA alloSCT following autologous stem cell transplant (ASCT) compared with ASCT alone for newly diagnosed HR-MM. Two-year progression-free survival was improved in the ASCT-NMA alloSCT group (44% vs 16%; $P = 0.035$), with a trend for improved overall survival ($P = 0.118$). These results suggest that ASCT-NMA alloSCT can be considered as upfront therapy in HR-MM.

Treatment of multiple myeloma (MM) has made remarkable progress over the past decade. The development of immunomodulatory drugs and proteasome inhibitors have improved patient outcomes and are now the mainstay of initial therapy. However, such agents have not improved outcomes in patients with high-risk (HR) features at diagnosis. The adverse outcomes in this group are also not abrogated by high-dose melphalan conditioned autologous stem cell transplant (ASCT).[1]

Allogeneic stem cell transplantation (alloSCT) utilises the graft-versus-myeloma (GVM) effect and offers the possibility of cure. Early experience with alloSCT demonstrated a prohibitively high rate of transplant-related mortality (TRM) ranging from 40% to 60%.[2] Subsequently, non-myeloablative allograft (NMA) regimens were introduced and shown to reduce TRM while retaining the potential benefits of GVM. They have been combined with the cytoreductive and immunosuppressive capability of ASCT, potentially improving outcomes in HR-MM.[3] Several prospective trials have examined this ASCT-NMA alloSCT approach compared to tandem ASCT with conflicting results.[4–12] A meta-analysis combining six biological assignment trials with almost 1200 patients found no difference between the two approaches in either standard risk or HR-MM.[13] Evaluation of outcome data from these trials is problematic; however, as they differ in study design with varying conditioning regimens and inconsistent definitions of HR-MM. We performed a single-centre retrospective study of long-term outcomes in upfront ASCT-NMA alloSCT compared to ASCT-alone for newly diagnosed HR-MM.

We reviewed the case records of all MM patients undergoing ASCT over a 10-year period between 2008 and 2018 at The Alfred Hospital, Melbourne. Patients with HR-MM treated with an upfront tandem ASCT-NMA alloSCT were identified and compared with a HR-MM cohort treated with ASCT-alone. HR disease was defined as having two or more of the following five factors: adverse cytogenetics, International Staging Score III, elevated lactate dehydrogenase, plasma cell leukaemia and induction failure (less than a partial response with protreasome inhibitor or immunomodulator based therapy). Adverse cytogenetics was defined as a complex karyotype on metaphase analysis and/or a high-risk lesion including t(4:14), t(14:16), del(17p) or gain (1q) by fluorescent *in situ* hybridisation (FISH). The additive effects of multiple FISH lesions were considered by

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attributing 1 HR score for each abnormality. The policy at our institution was to offer all fit HR-MM patients with an upfront ASCT-NMA alloSCT. Patients in the ASCT-alone group did not proceed to NMA alloSCT for a variety of reasons, including lack of human leukocyte antigen-matched donor, patient preference and geographical considerations. The ASCT-alone cohort was age matched with upfront ASCT-NMA alloSCT patients and excluded those aged over 65 years old. Patients who received any maintenance therapy after ASCT were excluded. Patients who received ASCT-NMA alloSCT at relapse as a deferred strategy were also excluded.

All ASCTs were conditioned with melphalan 140 or 200 mg/m^2 on day −1, followed by an infusion of granulocyte colony-stimulating factor mobilised peripheral blood stem cells on day 0. NMA alloSCT received conditioning in an outpatient setting as previously described.[3] Oral fludarabine 48 mg/m^2 was administered on days −4

Table 1 Baseline characteristics of high-risk multiple myeloma patients treated with autologous stem cell transplant (ASCT) non-myeloablative allograft (NMA) allogeneic stem cell transplantation (alloSCT) and ASCT alone

	ASCT-NMA alloSCT (n = 25), n (%)	ASCT-alone (n = 17), n (%)	P-value
Sex			
Male	13 (50)	11 (65)	0.530
Female	12 (46)	6 (35)	
Age (years)			
Median	55	54	0.714
Range	41–70	46–65	
Subtype			
IgG	10 (38)	8 (47)	0.390
IgA	6 (23)	5 (29)	
Light chain	5 (19)	4 (24)	
Non-secretory	4 (15)	0 (0)	
ISS stage			
I	4 (15)	0 (0)	0.220
II	7 (27)	6 (35)	
III	14 (54)	11 (65)	
Complex karyotype			
Yes	9 (35)	9 (53)	0.531
No	7 (27)	3 (18)	
Unknown	9 (35)	5 (29)	
No. high-risk FISH lesions			
2	1 (4)	1 (6)	0.347
1	14 (54)	5 (29)	
0	5 (19)	7 (41)	
Unknown	5 (19)	4 (24)	
High risk factors			
2	16 (62)	14 (82)	0.121
3	9 (35)	2 (12)	
≥ 4	0 (0)	1 (6)	
Disease status at ASCT			
CR	1 (4)	1 (6)	0.261
VGPR	4 (15)	5 (29)	
PR	11 (42)	8 (47)	
MR	2 (8)	0 (0)	
SD	5 (19)	0 (0)	
PD	2 (8)	3 (18)	
Donor type			
Sibling	9 (35)		
Unrelated	16 (62)		
Time from diagnosis to ASCT (months)			
Median	7.2	9.1	0.088
Range	3.3–16.2	4.1–23.1	

ASCT, autologous stem-cell transplantation; CR, complete response; FISH, fluorescent *in situ* hybridisation; ISS, International staging score; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

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to −2, followed by 2 Gy total body irradiation on day 0. Graft-versus-host disease (GVHD) prophylaxis consisted of mycophenolate and cyclosporine, and continued, in the absence of GVHD, until day 27 and 56 for sibling donors, or 96 and 180 for unrelated donors respectively.

Disease evaluation with bone marrow biopsy was routinely performed after alloSCT every 3 months in the first year, 6 months in the second year and then yearly thereafter. Patients in the ASCT-alone group had bone marrow assessments performed 3 months after transplant. Minimal residual disease (MRD) evaluation was performed using the eight-colour EuroFlow MM panel (Beckman Coulter, Brea, CA, USA) with a test sensitivity of 10^{-5} (<0.001%) requiring a minimum of 50 positive events.[14] This was incorporated into routine post-transplant evaluation at our institution from 2014 onwards.

Outcomes measured were progression-free survival (PFS), overall survival (OS), cumulative incidence of relapse (CIR) and TRM. These were measured from the time of ASCT. The rates of acute and chronic GVHD were also determined. OS and PFS curves were constructed using the Kaplan–Meier method, with analysis using the log-rank test. Cumulative incidences of CIR and TRM were calculated using Gray test for competing risks. Fisher exact test and chi-squared tests were used. Statistical analyses were performed using GraphPad Prism version 8.4.3 (San Diego, CA, USA) and R version 3.6.3 (R Development Core Team, 2020).

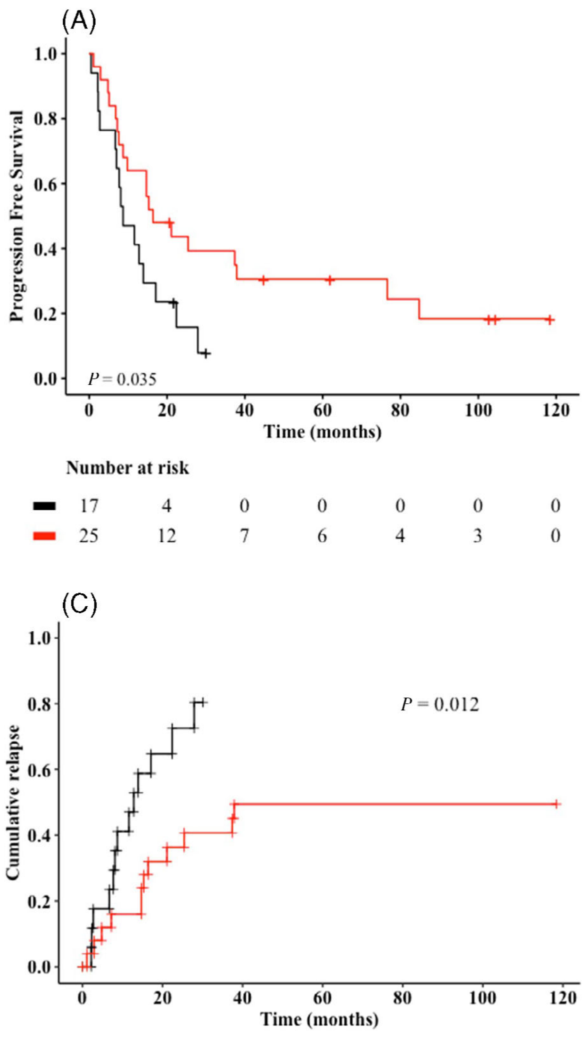

Figure 1 High-risk multiple myeloma treated with autologous stem cell transplant (ASCT) non-myeloablative allograft (NMA) allogeneic stem cell transplantation (alloSCT) compared with ASCT alone. (A) Progression-free survival; (B) overall survival; (C) relapse rate; (D) treatment-related mortality. (—+—), ASCT-alone; (—+—), ASCT-NMA alloSCT.

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Over a 10-year period between 2008 and 2018, 25 patients with HR-MM were treated with upfront ASCT-NMA alloSCT at The Alfred Hospital, Melbourne. We identified 17 HR-MM patients aged up to 65 years treated with ASCT-alone. Patient characteristics are described in Table 1. Median age was similar between the ASCT-NMA alloSCT and ASCT-alone groups (55 vs 54 years; $P = 0.797$).

Median follow up was 102.8 and 39.6 months for the ASCT-NMA alloSCT and ASCT-alone groups respectively. Outcomes are shown in Figure 1. PFS was significantly improved in the ASCT-NMA alloSCT group with 2-year PFS being 44% (95% confidence interval (CI) 24–62) compared with 16% (95% CI 3–37) in the ASCT-alone group ($P = 0.035$). There was trend for improved OS with ASCT-NMA alloSCT ($P = 0.118$).

CIR was significantly decreased in the ASCT-NMA alloSCT group ($P = 0.012$) with a 2-year CIR of 36% (95% CI 26–46) compared with 73% (95% CI 60–86). Relapse did not occur in 13 (52%) patients in the ASCT-NMA alloSCT arm. In this group, MRD negativity was evaluated in 10 patients. Durable negativity beyond 2 years was observed in seven (70%) cases. The 2-year cumulative incidence of TRM was 20% (95% CI 12–32) in the ASCT-NMA alloSCT compared with 12% (95% CI 4–20). Late TRM was high in the ASCT-NMA alloSCT group, approaching 32% (95% CI 12–43) at 100 months. GVHD was directly contributory in approximately half of these cases. Grade II–IV acute GVHD occurred in six (24%) of 25 patients, while extensive chronic GVHD occurred in 13 (52%) of 25 patients.

Discussion

Identification of HR-MM opens up the possibility of risk-adapted therapy.[15] Our single-centre study demonstrates the benefits of a tandem ASCT-NMA alloSCT approach in these patients. PFS was significantly improved in patients receiving upfront ASCT-NMA alloSCT compared to ASCT-alone. CIR was significantly decreased with few relapses occurring beyond 24 months. The majority of ASCT-NMA alloSCT patients were in durable MRD negative remission beyond this point.

Adverse cytogenetics are important in defining HR-MM, with an updated consensus by the International Myeloma Working Group including t(4;14), t(14;16), t(14;20), del(17/17p) and gain(1q) by FISH, as well as del(13) and non-hyperdiploidy on karyotyping.[16] The poor prognosis of these lesions has been confirmed in large-scale meta-analyses, with co-occurrence of two or more being additive and conferring a worst outcome.[17] Our definition of HR-MM reflects these cytogenetic aberrations. This is in contrast to several prospective trials of ASCT-NMA alloSCT where HR disease was defined using less robust prognostic factors, diluting any potential benefit. For instance, the Intergroupe Francophone du Myelome (IFM) studies IFM99-03 and IFM99-04 as well as the BMT clinical trial network (CTN) 0102 trial defined HR as elevated β_2-microbulin and chromosome 13 deletion by FISH.[5,6,10] The German Deutschen Studiengruppe Multiples Myelom V trial defined HR disease in those with just chromosome 13 deletion alone.[11] While del(13) by karyotype predicts impaired PFS/OS,[18] del(13) by FISH as a single adverse lesion does not confer poor prognosis.[19]

In addition to adverse cytogenetics, our definition of HR-MM also included functional markers of poor prognosis. Using this, HR patients treated with ASCT alone in our study had poor outcomes equivalent to that reported in other studies with a median survival of 2–3 years.[2,17,20,21] These patients fared exceedingly poorly with a median PFS of 10.1 months, with more than half of patients relapsing within 12 months of their ASCT. While our comparison group did not receive maintenance therapy post-ASCT, single agent lenalidomide maintenance has not been shown to improve outcomes in HR disease.[22] We did analyse a small proportion of HR-MM patients treated with lenalidomide maintenance post-ASCT, which was not publicly funded at the time. This group had similar outcomes to HR-MM treated with ASCT-alone, albeit the numbers were too small ($n = 7$) for meaningful analysis.

Advantages of our study include uniform selection of HR patients for upfront ASCT-NMA alloSCT, all of whom received the same conditioning regimen, as well as a long follow-up period. Limitations of our study include small cohort numbers, retrospective design and inherent biases associated with a HR-MM group that did not proceed to NMA alloSCT. Our results demonstrate improved PFS and a trend for improved OS with a tandem ASCT-NMA alloSCT approach. Furthermore, relapse is significantly decreased with a high proportion of patients achieving MRD negativity. Late TRM was high in the ASCT-NMA alloSCT group, predominantly due to complications from GVHD. These competing benefits and risks should be individualised and discussed with the patient. Overall, these results suggest that upfront ASCT-NMA alloSCT may be beneficial in select patients with HR-MM; however, further evaluation in larger prospective trials is required.

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