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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Key words
multiple myeloma, transplant, high risk, allogeneic.

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).

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%. 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. Several prospective trials have examined this ASCT-NMA alloSCT approach compared to tandem ASCT with conflicting results. 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. 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 proteasome 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/m² 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. Oral fludarabine 48 mg/m² 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            | Female          | Male            | Female          | 0.530 |
|                  | 13 (50)         | 12 (46)         | 11 (65)         | 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.
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. 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.
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 β2-microbulbin 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 cytogentic criteria, 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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References

1 McCarthy PL, Holstein SA, Petrucci MT, Richardson PG, Hulin C, Tosi P et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. J Clin Oncol 2017; 35: 3279–89.

2 Kochne G, Giralt S. Allogeneic hematopoietic stem cell transplantation for multiple myeloma: curative but not the standard of care. Curr Opin Oncol 2012; 24: 720–6.

3 Campbell P, Walker P, Avery S, Patil S, Curtis D, Schwarer A et al. Safe and effective use of outpatient non-myeloablative allogeneic stem cell transplantation for myeloma. Blood 2014; 124: 4684.

4 Knop S, Liebsch P, Hebart H, Holler E, Engelhardt M, Metzner B et al. Autologous followed by allogeneic versus tandem-autologous stem cell transplant in newly diagnosed FISH-del13q myeloma. Blood 2016; 127: 2207–16.

5 Björkstrand B, Iacobelli S, Hegenbart U, Gruber A, Greinix H, Volin I et al. Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. J Clin Oncol 2011; 29: 5016–22.

6 Nair AP, Lee C, Kalff A, Walker PA, Bergin K, Hocking J et al. High risk multiple myeloma: better outcomes with upfront tandem autologous–non-myelo ablative allogeneic stem cell transplantation compared to upfront autologous stem cell transplantation. Blood 2016; 128: 80.

7 Krishnan A, Pasquini MC, Logan B, Stadtmauer EA, Vesole DH, Alyea E et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol 2011; 12: 1195–203.

8 Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood 2016; 127: 2955–62.

9 Shah V, Sherborne AL, Walker BA, Johnson DC, Boyle EM, Ellis S et al. Prediction of outcome in newly diagnosed myeloma: a meta-analysis of the molecular profiles of 1905 trial patients. Leukemia 2018; 32: 102–10.

10 Chiecchio L, Protheroe RKM, Ibrahim AH, Cheung KL, Rudduck C, Dagrada GP et al. Deletion of chromosome 13 detected by conventional cytogenetics is a critical prognostic factor in myeloma. Leukemia 2006; 20: 1610–17.

11 Boyd KD, Ross FM, Chiecchio L, Dagrada GP, Konn ZJ, Tapper WJ et al. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC myeloma IX trial. Leukemia 2012; 26: 349–55.

12 Kazmi SM, Nusrat M, Gunaydin H, Cornelison AM, Shah N, Kebriaei P et al. Outcomes among high-risk and standard-risk multiple myeloma patients treated with high-dose chemotherapy and autologous hematopoietic stem-cell transplantation. Clin Lymphoma Myeloma Leuk 2015; 15: 687–93.

13 Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L et al. Revised international staging system for multiple myeloma: a report from international myeloma working group. J Clin Oncol 2015; 33: 2863–9.

14 Shah V, Sherborne AL, Johnson DC, Ellis S, Price A, Chowdhury F et al. Predicting ultrahigh risk multiple myeloma by molecular profiling: an analysis of newly diagnosed transplant eligible myeloma XI trial patients. Leukemia 2020; 34: 3091–6.