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Title: Impact of minimal residual disease (MRD) in salvage autologous stem cell transplantation for relapsed myeloma: results from the NCRI Myeloma X (intensive) trial.

Ruth M de Tute PhD[1], Gordon Cook PhD[2], David A Cairns PhD[2], Julia M Brown MSc[2], Jamie Cavenagh MD[3], A John Ashcroft PhD[4], John A Snowden[5], Kwee Yong[6], Eleni Tholouli PhD[7], Matthew Jenner[8], Anna Hockaday BSc[2], Mark T Drayson PhD[9], Treen C M Morris MD[10], Andy C Rawstron PhD[1] & Roger G Owen MD[1]

[1] Haematological Malignancy Diagnostic Service, Leeds Teaching Hospitals Trust, UK
[2] Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds
[3] Department of Haematology, Barts & The London NHS Trust, UK
[4] Mid-Yorks NHS Trust, Wakefield, UK
[5] Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust & Department of Endocrinology & Metabolism, University of Sheffield, UK
[6] Department of Haematology, University College London, London, UK
[7] Department of Clinical Haematology, Manchester Royal Infirmary, Manchester Foundation Trust, Manchester, UK
[8] University Hospital Southampton NHS Foundation Trust, Southampton, UK
[9] Institute of Immunology and Immunotherapy University of Birmingham, UK
[10] College of Myeloma, UK

Laboratory research was performed at the HMDS laboratory at St James University Hospital, Leeds.

Corresponding author: Gordon Cook
E-mail: rdetute@nhs.net
Address: HMDS, Level 3, Bexley Wing, St James University Hospital, Leeds, LS9 7TF, UK
Telephone number: +44 113 2067851

Minimal residual disease (MRD) is a reproducible and independent predictor of both progression-free (PFS) and overall (OS) survival in multiple myeloma[1]. These data along with ever improving survival outcomes has led to consideration of MRD as a potential surrogate end point for regulatory purposes and an appropriate endpoint in academic studies which could accelerate evaluation of novel agents[2]. The value of MRD in myeloma has primarily been demonstrated in the upfront setting and following autologous stem cell transplantation (ASCT) in particular[3]. Improving survival is increasingly reported in the relapse setting and here we examine the role of MRD (assessed by multi parameter flow cytometry) in first relapse following prior autologous stem cell transplantation (ASCT) in the context of the NCRI Myeloma X (intensive) trial

The NCRI Myeloma X (intensive) trial was a randomized, multicenter, phase III trial for which the study protocol and clinical results have been previously described[4,5]. The protocol was approved by the relevant institutional review boards and all patients provided written informed consent. Eligible patients with progressive or relapsed disease requiring treatment after a first ASCT with durable response (>12 months) who completed re-induction chemotherapy with bortezomib, adriamycin and dexamethasone (PAD) were randomized to receive either salvage ASCT or non-transplant consolidation (NTC: oral cyclophosphamide in 12 weekly cycles). Bone marrow aspirates were obtained after re-induction and at day 100 after salvage ASCT or 30 days after completion of NTC for comparability. Flow cytometric analysis was performed by a single laboratory using a previously published methodology with a lower limit of detection (LOD) of 0.004%[6]. Statistical analysis was also performed as reported previously, with time to progression (TTP) and OS data landmarked to the date of the MRD assessment

rather than the date of randomisation. In exploratory multivariable analysis, the prognostic potential of MRD for these end points was assessed adjusting for patient age at trial entry, sex, international staging system (ISS; I vs II vs III), durability of response after first ASCT (<18 vs ≥18 months) and whether or not stem cell mobilization was performed on trial (yes vs no).

A total of 297 patients were registered into the study and 174 were randomly assigned to salvage ASCT or NTC (see Table 1. for baseline characteristics). The median follow-up was 52 months. Previously reported clinical results demonstrated a significant TTP and OS advantage in favour of ASCT (hazard ratios (HR) 0.45 (95% confidence interval [CI] 0.31–0.64) and 0.52 (95% CI 0.31–0.64), respectively)[4,5]. Adequate follow-up bone marrow aspirate samples were obtained from 162 patients following re-induction and 95 patients following consolidation (47 salvage ASCT; 48 NTC).

Of 162 evaluable samples received post re-induction, 44 (27%) were classified as MRD-negative. For those cases which were MRD-positive, residual neoplastic-phenotype plasma cells (neo-PC) represented a median of 0.33% of BM leucocytes (range 0.01%-28%).

Following randomization to salvage ASCT, 25 (53%) of 47 evaluable patients were MRD-negative and in those classified MRD-positive residual neo-PC represented a median of 0.29% of BM leucocytes (range 0.005%-6.4%). For those patients randomized to NTC, 19 (40%) of 48 evaluable patients were MRD negative, with MRD-positive patients demonstrating a median neo-PC population of 0.32% of BM leucocytes (range 0.02%-18%). The higher proportion of MRD-negative patients seen in the salvage ASCT group is not statistically significant (Fisher's Exact Test p= 0.2196), but the trend is consistent with the outcome advantage in response, TTP and OS seen in that group as a whole.

In this relapse cohort MRD had a significant impact on survival outcomes. The median TTP for those patients who were MRD-negative post ASCT / NTC was 21 months (95% CI 12–25) compared to 7 months (95% CI 6–8) for MRD-positive patients (HR 0.37; 95% CI 0.24–0.59; p<0.0001). Median OS for MRD-negative patients was 67 months (95% CI 45–NR) compared

to 51 months (95% CI 37–61) for MRD-positive patients (HR 0.49; 95 CI 0.26–0.92; p=0.0245) (Figure1.) Multivariable analysis including randomized allocation, MRD status and other factors detailed above demonstrated that MRD status and treatment response duration following first-line therapy were the only factors which were independently prognostic for TTP (p=0.0043 and 0.0014 respectively). Previous treatment response duration was the only variable to retain statistical significance (p=0.0458) in similar analysis of OS. The prognostic significance of MRD was demonstrable in both ASCT and NTC patients for TTP, with no evidence of heterogeneity of prognostic potential of MRD status by allocated consolidation treatment (Figure 2) (Cox model interaction test, P = 0.6834). This was also true for OS (Cox model interaction test, P = 0.7456).

The impact of post induction MRD was also evaluated in 75 patients with sequential assessments. Outcome was principally determined by the post consolidation MRD status with patients who were positive following re-induction and then negative following consolidation having TTP outcome similar to those negative at both time points. This is in contrast to similar studies in the upfront setting where outcome appeared best in those patients achieving MRD negativity early[3,6]. A small number of patients in this analysis had no detectable disease post-induction and subsequently converted to MRD-positivity following further therapy and these had a poor outcome consistent with previous studies[7].

Survival outcomes continue to improve in myeloma. Improvements have been specifically noted in the relapse setting with the use of novel combinations, including carfilzomib, ixazomib, pomalidomide and monoclonal antibodies[8-10]. Similarly, the Myeloma X trial has shown that salvage ASCT is associated with survival benefits and is an attractive option for a suitable cohort of myeloma patients[4,5]. These data suggest it is appropriate to consider MRD in the relapse / refractory as well as upfront setting. In this context Paiva and colleagues evaluated 52 patients achieving serological complete response (CR) following re-induction therapy. A significant outcome advantage was noted for those patients achieving MRD negativity with the exception of those undergoing allogeneic bone marrow transplant[11]. The lack of prognostic impact in the allogenic transplant setting appeared to be as a consequence

of a high incidence of extramedullary relapse. In a more recent analysis highly sensitive next generation sequencing (NGS) has been used to evaluate MRD in patients treated with daratumumab-based combinations. These demonstrated that MRD negative responses, below 10^{-5} residual myeloma cells, was possible in the relapse setting and that this had a significant impact on PFS[12]. A further conclusion made from this and other studies was that the impact of MRD negativity is independent of therapy received with outcomes determined by levels of residual disease rather than treatment received. This is clearly a key criterion if MRD is to be used as a surrogate or intermediate survival endpoint by regulatory authorities. We would conclude that MRD is an independent predictor of outcome in relapsed myeloma with a similar magnitude of benefit to that seen in the upfront setting. Novel therapies are producing high rates of complete response resulting in extended survival outcomes in relapsed disease. MRD should be assessed prospectively in all myeloma trials regardless of line of therapy.

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The study was approved by the national ethics review board (Multicentre Research Ethics Committee, UK, institutional review boards of the participating centers, approved by the competent regulatory authority (Medicines and Healthcare Products Regulatory Agency, UK) and was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Author contributions

Research design: Ruth M. de Tute, Gordon Cook, Roger G. Owen

Provision of study materials or patients: Gordon Cook, Jamie Cavenagh, John Ashcroft, John A Snowden, Cathy Williams, Kwee Yong, Eleni Tolouli, Matthew Jenner, Treen C M Morris, Roger G. Owen

Collection and assembly of data: Ruth M. de Tute, David A Cairns, Anna Hockaday, Mark T. Drayson, Andy C. Rawstron, Roger G. Owen

Data analysis and interpretation: Ruth M. de Tute, Gordon Cook, David A Cairns, Julia M Brown, Mark T. Drayson, Andy C. Rawstron, Roger G. Owen

Manuscript writing: All authors

Final approval of manuscript: All authors

Conflicts of interest

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Table 1: Baseline Characteristics of those without MRD analysis and those with MRD analysis following randomised treatment split by randomised treatment

	No MRD analysis	With MRD analysis		Total
	All patients	C-weekly	HDM & ASCT	
Age at registration				
Mean (s.d.)	60 (6.9)	59 (7.0)	59 (7.4)	59 (7.0)
Patients gender				
Male	49 (62.0%)	37 (77.1%)	40 (85.1%)	126 (72.4%)
Female	30 (38.0%)	11 (22.9%)	7 (14.9%)	48 (27.6%)
Patients race				
White	70 (88.6%)	46 (95.8%)	45 (95.7%)	161 (92.5%)
Asian - Indian	1 (1.3%)	2 (4.2%)	0 (0.0%)	3 (1.7%)
Asian - Pakistani	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Other Asian background	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Black - Caribbean	2 (2.5%)	0 (0.0%)	1 (2.1%)	3 (1.7%)
Black - African	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Other Black background	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Not stated	2 (2.5%)	0 (0.0%)	1 (2.1%)	3 (1.7%)
Paraprotein Type at Diagnosis				
IgG	57 (72.2%)	32 (66.7%)	28 (59.6%)	117 (67.2%)
IgA	12 (15.2%)	10 (20.8%)	9 (19.1%)	31 (17.8%)
IgM	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
IgD	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (0.6%)
Light chain only	5 (6.3%)	4 (8.3%)	5 (10.6%)	14 (8.0%)
Non-secretor	2 (2.5%)	1 (2.1%)	2 (4.3%)	5 (2.9%)
Missing	2 (2.5%)	0 (0.0%)	3 (6.4%)	5 (2.9%)
Lightchain Type at Diagnosis				
Lambda	18 (22.8%)	14 (29.2%)	13 (27.7%)	45 (25.9%)

	No MRD analysis	With MRD analysis		Total
	All patients	C-weekly	HDM & ASCT	
Kappa	52 (65.8%)	32 (66.7%)	27 (57.4%)	111 (63.8%)
Missing	9 (11.4%)	2 (4.2%)	7 (14.9%)	18 (10.3%)
ISS at Registration Baseline				
I	48 (60.8%)	29 (60.4%)	31 (66.0%)	108 (62.1%)
II	13 (16.5%)	15 (31.3%)	11 (23.4%)	39 (22.4%)
III	9 (11.4%)	0 (0.0%)	3 (6.4%)	12 (6.9%)
Missing	9 (11.4%)	4 (8.3%)	2 (4.3%)	15 (8.6%)
Randomisation treatment				
HDM & ASCT	42 (53.2%)	47 (100%)	0 (0.0%)	89 (51.1%)
C-weekly	37 (46.8%)	0 (0.0%)	48 (100%)	85 (48.9%)
Total	79 (100%)	47 (100%)	48 (100%)	174 (100%)

Fig. 1 Outcome according to minimal residual disease (MRD)

Presence of MRD at the end of treatment was associated with inferior outcome: (A) time to progression (TTP); $p<0.0001$; (B) overall survival (OS); $p = 0.025$

Fig. 2 Prognostic significance of MRD is independent of treatment received

Patients achieving MRD negativity, both post sASCT (HDM and ASCT) and following NTC (C-weekly), had a superior TTP relative to MRD positive patients (TTP; $p<0.0001$)

HDM, high-dose melphalan; ASCT, autologous stem cell transplant; C-weekly, oral cyclophosphamide weekly