Institution: University of Leeds

Unit of Assessment: UOA1 Clinical Medicine

Title of case study:
Case Study 6. Transforming the treatment of myeloma has produced significant improvement in patient survival: the MRC Myeloma trials

1. Summary of the impact

Two large multicentre clinical trials designed and led by researchers and clinicians in Leeds have resulted in major changes to treatment for patients with multiple myeloma. Myeloma VII clearly established the use of high-dose melphalan supported by autologous stem cell transplant (ASCT) following chemotherapy. Myeloma IX, the largest randomised controlled trial ever in myeloma, showed that zoledronic acid, in addition to reducing skeletal damage, showed an overall survival benefit and introduced the use of thalidomide as an effective yet less toxic therapy. Adoption of these treatment regimens has produced significantly improved outcomes throughout the developed world.

2. Underpinning research

Multiple myeloma is a malignant disease of bone and bone marrow that causes pain and disability and in the majority of patients is fatal. Conventional chemotherapy had only a modest impact on survival. **Peter Selby** (Professor of Cancer Medicine, Leeds 1989-) contributed to early laboratory studies on high-dose chemotherapy in the 1980s at the Royal Marsden Hospital, London. On moving to Leeds, Selby collaborated with **Anthony Child** (Leeds 1974-, Honorary Professor of Haematology, Leeds 2002-) and **Gareth Morgan** (Professor of Haematology, Leeds 1990-2006) to initiate and lead a key RCT (MRC Myeloma VII) evaluating both the clinical impact of high-dose chemotherapy using melphalan and the addition of autologous stem cell transplant (1). The trial was designed and delivered through the Leeds Clinical Trials Research Unit, CTRU (**Julia Brown**, Professor of Clinical Trials Research, Leeds 1990-, **Walter Gregory**, Professor of Statistical Methodology in Clinical Trials, Leeds 2005-, **S Bell**, Leeds 1998-, **K Hawkins**, Leeds 2001-2010, and **R Owen**, Leeds 1998-, Principal Research Fellows, Leeds). MRC Myeloma VII provided for the first time conclusive evidence that high-dose chemotherapy was effective for myeloma. It showed that high-dose chemotherapy improved survival for patients under 65 years of age by 5% at five years, a finding which was confirmed by a meta-analysis with a simultaneous French trial (1).

Building on this evidence, MRC Myeloma IX, also initiated and designed in Leeds and run by the Leeds CTRU (**Child, Gordon Cook**, Honorary Professor of Haematology and Myeloma Studies, 2003- , **Morgan, Brown** and **Gregory**), used the now proven treatments of high-dose chemotherapy with melphalan and ASCT but with the addition of novel oral agent thalidomide to overcome toxicity associated with regimens involving parenteral infusional chemotherapy. The trial showed thalidomide to be an effective oral induction therapy for multiple myeloma associated with fewer toxic effects and has since become primary treatment of choice (4,5,6).

Myeloma IX also included a new third-generation bisphosphonate to assess the control of bone damage. Patients were randomised to receive newer drug zoledronic acid or standard bisphosphonate treatment to determine both the anti-osteolytic effects but also possible survival difference. It showed not only that zoledronic acid significantly reduced bone damage in comparison with the previous standard bisphosphonate, clodronate, but also is associated with better survival (2). This too is now considered a standard treatment for multiple myeloma. The six-year median follow-up analysis continued to indicate a late survival benefit. Analyses have shown this is not dependent on the drug's effect in preventing or delaying bone recurrence, and zoledronic acid may have a previously unsubstantiated direct anti-myeloma effect (2,3,4,5,6).

The trial also evaluated thalidomide in the maintenance setting and showed benefits of its use to maintain the effects of initial chemotherapy – a strategy now widely used (5). Importantly Myeloma IX included older less fit patients in a non-intensive treatment pathway – a large group clinically but one previously excluded in the trial setting. Treatment incorporating thalidomide appeared to provide a significant benefit in older, less fit patients, with a suggestion of an emerging survival benefit for those patients surviving more than 2 years (4, 5).

3. References to the research

(1) **Child JA**, **Morgan GJ**, Davies FE, **Owen RG**, **Bell SE**, **Hawkins K**, **Brown J**, Drayson MT, **Selby PJ** for the Medical Research Council Adult Leukaemia Working Party. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003; 348: 1875-1883.
This trial led by Child and Selby and performed through Leeds CTRU shows that high-dose chemotherapy with stem cell rescue is better than conventional therapy and led to the use of this treatment strategy for young patients with multiple myeloma across the world.

(2) Morgan GJ, Davies FE, **Gregory WM**, Cocks K, **Bell SE**, Szubert AJ, Navarro-Coy N, Drayson MT, **Owen RG**, **Feyler S**, Ashcroft AJ, Ross F, Byrne J, Roddie H, Rudin C, **Cook G**, Jackson GH, **Child JA**, National Cancer Research Institute Haematological Oncology Clinical Study Group. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet 2010; 376: 1989-1999.
This trial led by Child as Chief Investigator and performed through Leeds CTRU shows the superiority of zoledronic acid in reducing bone damage in myeloma patients and improving their survival and has been adopted into therapy.

(3) Morgan GJ, **Child JA**, **Gregory WM**, Szubert AJ, **Cocks K**, **Bell SE**, Navarro-Coy N, Drayson MT, **Owen RG**, Feyler S, Ashcroft AJ, Ross FM, Byrne J, Roddie H, Rudin C, **Cook G**, Jackson GH, Wu P, Davies FE, National Cancer Research Institute Haematological Oncology Clinical Studies Group. Effects of zoledronic acid versus clodronic acid on skeletal morbidity in patients with newly diagnosed multiple myeloma (MRC Myeloma IX): secondary outcomes from a randomised controlled trial. Lancet Oncol 2011; **12**(8): 743-752.
This paper further analysed Myeloma IX trial showing improved survival not only as a result of delaying damage to bone but possibly because of a direct effect on the tumour.

(4) Morgan GJ, Davies FE**, Gregory WM**, Russell NH, **Bell SE**, Szubert AJ, Navarro Coy N, **Cook G**, **Feyler S**, Byrne JL, Roddie H, Rudin C, Drayson MT, **Owen RG**, Ross FM, Jackson GH, **Child JA**, NCRI Haematological Oncology Study Group. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. Blood 2011; 118: 1231-1238.
In Myeloma IX the use of a simpler initial therapy at the beginning of therapy was shown to be effective and has been widely adopted.

(5) Morgan GJ, **Gregory WM**, Davies FE, **Bell SE**, Szubert AJ, **Brown JM**, Coy NN, **Cook G**, Russell NH, Rudin C, Roddie H, Drayson MT**, Owen RG**, Ross FM, Jackson GH, **Child JA**; National Cancer Research Institute Haematological Oncology Clinical Studies Group. Blood. 2012; 119: 7-15. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis.
In Myeloma IX benefits were shown from the use of a simple oral therapy to maintain the effects of the initial chemotherapy. This is widely used.

(6) Morgan GJ, Davies FE, **Gregory WM**, **Bell SE**, Szubert AJ, **Cook G**, Drayson MT, **Owen RG**, Ross FM, Jackson G, **Child JA**. Long-Term Follow-Up of MRC Myeloma IX Trial: Survival Outcomes with Bisphosphonate and Thalidomide Treatment. Clin Cancer Res. 2013 Aug 30.
This paper confirms the long term impact of zoledronic acid and thalidomide.

4. Details of the impact

The use of high-dose melphalan with autologous stem cell rescue and associated combination chemotherapies was a novel clinical intervention which was shown in a trial initiated and led from Leeds and run by the Leeds CTRU (Myeloma VII) to significantly improve outcomes in patients with multiple myeloma (1). The addition of thalidomide and zoledronic acid were shown in a subsequent RCT (Myeloma IX), the largest ever conducted in myeloma, to further improve patient outcome (2). Together this work has transformed the standard management of myeloma.

Impact on health and welfare

The results of Myeloma VII – that high-dose chemotherapy with ASCT was a significant improvement on standard chemotherapy – was incorporated in UK clinical guidelines, with Morgan and Cook as advisors [A] and international Guidelines [B]. This led to widespread changes in practice as shown by an increase in the uptake of high-dose therapy with autologous stem cell transplants in the UK in the treatment of multiple myeloma rising from 211 in 1999 to 453 in 2005, the increase being sustained in 2008 – 2013 [C, D]. These changes were also seen internationally with a doubling of use of this treatment between 2003 (publication of Myeloma VII) and most recent data for all Europe in 2010 [E].

The latest cancer survival statistics for patients diagnosed in the period 2005-2009 with their period of survival followed throughout the REF Impact period (2008-2013) show large improvements in survival. In men, one-year relative survival rates for myeloma increased from 35.2% during 1971-1975 to 70.4% during 2005-2009. In women, one-year relative survival rates increased from 40.6% to 72.3% during the same time periods [F]. Meta analysis suggests that the use of high-dose melphalan with ASCT will improve longer term survival in young myeloma patients (1). This is supported by figures which show ten-year relative survival rates for men diagnosed with myeloma increased from 5.3% during 1971-1975 to a predicted 19% in those diagnosed in 2007. In women, ten-year relative survival rates increased from 4.8% to a predicted 14.9% during the same time periods [F].

Cancer Research UK, the external agency responsible for this analysis say that high-dose treatment is an important component in this improvement in mortality [F]. They observe ***"the most marked improvements in five- and ten-year survival have happened since the early 1990s, probably reflecting the effective and widespread use of high-dose chemotherapy and autologous stem cell transplantation".*** This was substantially and materially a consequence of Leeds research (Myeloma VII). They add that more recent advances in biological therapies including the use of thalidomide (Myeloma IX) mean that survival rates are continuing to improve rapidly and ***"current data may underestimate the survival rates for myeloma patients diagnosed today"*** [F]. Within the UK healthcare system, recommendations for intensive therapy and for appropriate quality assurance of units delivering this treatment have been developed. Changes in healthcare professional training and professional standards in competence and safety and have been implemented for this treatment [A].

The importance of zoledronic acid in myeloma, as shown by Myeloma IX, has been noted by reviewers [G,H] and incorporated into professional guidelines in the USA, Canada and Europe-wide, which recommended that "given the recent data from the Myeloma IX trial, zoledronic acid is the bisphosphonate of choice in multiple myeloma" [H,I]. The use of zoledronic acid in myeloma patients in the UK has increased. An independent survey of leading physicians and researchers working in myeloma voted the results on the efficacy of zoledronic acid as the most important publication on myeloma in 2010 [G]. The British Society Committee for Standards in Haematology and the UK Myeloma Forum recommended that zoledronic acid should be given to all patients who have symptomatic multiple myeloma referencing Myeloma IX [A]. The study has also influenced clinical guidelines recommending the use of thalidomide [A,B,I,J]. Subsequent prescribing data from the UK shows uptake has increased as use the drug has become widespread in clinical practice [K]. Leading international opinion confirms the attribution of changes in myeloma practice and outcomes to Leeds research and the MRC Myeloma trials conducted by the Leeds CTRU and led substantially by Leeds based clinical investigators [L].

5. Sources to corroborate the impact

(A) JM Bird, RG Owen, S D'Sa, J Snowden, G Pratt, J Ashcroft, K Yong, G Cook, S Feyler, FE Davies, GJ Morgan, J Cavenagh, E Low, J Behrens. (2011) NICE Guidelines on Myeloma Management. Guidelines for the diagnosis & management of multiple myeloma 2010. British Journal of Haematology; 154: 32-75. *NICE guidelines clearly indicate that high-dose chemotherapy with autologous stem cell rescue is indicated for younger patients with myeloma and refers to the Myeloma VII trial.*

(B) Cavo et al. International Myeloma Working Group consensus approach to the treatment of

multiple myeloma patients who are candidates for autologous stem cell transplantation. Blood 2011; 117: 6063-73. *International Myeloma Working Group Guidelines indicate the value of high-dose treatment and stem cell rescue in young patients and reference the Leeds Myeloma VII data.*

(C) Cook G, Jackson GH, Morgan GJ, Russell NH, Kirkland K, Lee J, Marks DI & Pagliuca A. The outcome of high dose chemotherapy and autologous stem cell transplantation (ASCT) in patients with multiple myeloma: a comparison between two decades and benchmarking against European outcomes. Bone Marrow Transplantation 2011; 46: 1210-18.
The UK Transplant Society data shows increasing use of autologous stem cell approaches in myeloma rising from 211 in 1999 to 453 in 2005.

(D) British Society for Bone Marrow Transplantation provides by Kieran Kirkland, Head of Data Registry. *Myeloma Registry data show increasing uptake of intensive therapy with autologous stem cell support during and after publication of Myeloma VII from Leeds, sustained through to impact period 2008-2013.*

(E) European Group for Blood and Marrow Transplantation Annual Report 2011, p7. *This report summarises all EBMT activity. For myeloma high dose therapy with stem cells rise from c 4,000 cases in 2003 to c 8,000 cases in 2010.*

(F) Cancer Research UK data on changing survival in myeloma.
http://www.cancerresearchuk.org/cancer-info/cancerstats/types/myeloma/survival/multiple-myeloma-survival-statistics

(G) The Myeloma Beacon survey of most important publications in the field in 2010. Full details at:
http://www.myelomabeacon.com/news/2011/03/16/the-top-multiple-myeloma-research-of-2010/
This gives an international authoritative view on the impact of Myeloma IX on clinical practice.

(H) Richardson PG, Laubach JP, Schlossman RL, Ghobrial IM, Mitsiades CS, Rosenblatt J, Mahindra A, et al. (2011). The Medical Research Council Myeloma IX trial: the impact on treatment paradigms*. European Journal of Haematology, Myeloma IX: changing treatment paradigms?, 88(1), 1–7. *The review summarises the conclusive impact of Myeloma IX and its incorporation into guidelines for clinical practice in the USA, Canada and Europe.*

(I) Clinical Guidelines in Canada (Reece D, Sebag M, White D, Song K. A Canadian perspective on the use of bisphosphonates in the clinical management of multiple myeloma. New Evidence in Oncology, March 2011), the USA (National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. v.1.2014. Fort Washington, PA: National Comprehensive Cancer Network Inc, 2013) and Europe-wide (Terpos E, Sezer O, Croucher PI, García-Sanz R, Boccadoro M, San Miguel J, Ashcroft J, Bladé J, Cavo M, Delforge M, Dimopoulos MA, Facon T, Macro M, Waage A, Sonneveld P; European Myeloma Network. The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network. Ann Oncol. 2009 Aug;20(8):1303-17).

(J) NICE technology appraisal guidance 228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. 2011. http://publications.nice.org.uk/bortezomib-and-thalidomide-for-the-firstline-treatment-of-multiple-myeloma-ta228
This NICE technology appraisal supports the use of thalidomide in the treatment of myeloma indicating the impact of Myeloma IX on clinical practice.

(K) NHS Zoledronic acid and thalidomide prescribing data. *NHS Zoledronic acid prescribing data for myeloma shows a doubling of prescriptions following the 2011 publication. Thalidomide prescriptions rose during Myeloma IX and were sustained after the trial publication. Data provided by Cellgene.*

(L) Letter of corroboration from Dr Stewart, Mayo Clinic, the leading US authority on myeloma.