
# WORKING GROUP ON ACUTE PURCHASING

# The Effectiveness of High Dose Chemotherapy and Bone Marrow/Autologous Stem Cell Transplantation in the Treatment of Multiple Myeloma

## October 1998


## GUIDANCE NOTE FOR PURCHASERS 98/08

**Series Editor: Nick Payne**

**InterDEC Report No. 19/1998**

# Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 20 October 1998 at which this Guidance Note for Purchasers (in a draft form) was considered.

## THE EFFECTIVENESS OF HIGH DOSE CHEMOTHERAPY AND BONE MARROW /AUTOLOGOUS STEM CELL TRANSPLANTATION IN THE TREATMENT OF MULTIPLE MYELOMA

**AUTHORS:** Beard S M, Sampson F C, Scott F and Vandenberghe E. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1998. Guidance Note for Purchasers: 98/08.

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Dr A Hunter, Consultant Haematologist, Leicester Royal Infirmary.

*(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts.)*

**DECISION: The Committee recommended that high dose chemotherapy should be made available for suitable patients. Those with a health status equivalent to, or better than, an average 65 year old, with good performance status and stage II/III disease, should be offered high dose chemotherapy and autologous transplantation. Those with a health status equivalent to, or better than, an average 50 year old should be offered high dose chemotherapy and allogeneic transplantation within appropriate controlled trials or follow up studies.**

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***Conflict of Interest*** None of the authors of this document has any financial interests in the drug or product being evaluated here.

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## ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides a consultancy service to NHS bodies on service problems;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

## FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority and Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development, The Scottish Health Purchasing Information Centre (SHPIC) and The University of Birmingham Department of Public Health and Epidemiology.

**Professor R L Akehurst**
**Chairman, Trent Working Group on Acute Purchasing**

## ABBREVIATIONS

| | |
|---|---|
| **ABMT** | Autologous Bone Marrow Transplantation |
| **ALL** | Acute Lymphoblastic Leukaemia |
| **alloBMT** | Allogeneic Bone Marrow Transplantation |
| **AML** | Acute Myeloid Leukaemia |
| **BMT** | Bone Marrow Transplantation |
| **BSBMT** | British Society for Blood and Marrow transplantation |
| **BVAP** | Vincristine/Carmustine/Doxorubicin/Prednisolone |
| **CML** | Chronic Myeloid Leukaemia |
| **EBMT** | European Blood and Marrow Transplant Registry |
| **HDC** | High Dose Chemotherapy |
| **HLA** | Human Leukocyte Antigen |
| **HTA** | Health Technology Assessment |
| **IFM** | Intergroupe Francais du Myelome |
| **Ig** | Immunoglobulin |
| **LYG** | Life Year Gained |
| **MRC** | Medical Research Council |
| **NHL** | Non-Hodgkin's Lymphoma |
| **ONS** | Office of National Statistics |
| **PBCT** | Peripheral Blood Stem Cell Transplantation |
| **PIS** | Patient Information System |
| **SWOG** | Southwest Oncology Group |
| **VAD** | Vincristine/Doxorubicin/Dexamethasone |
| **VAMP** | Vincristine/Adriamycin/Methylprednisolone |
| **VMCP** | Vincristine/Melphalan/Cyclophosphamide/Prednisolone |

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## EXECUTIVE SUMMARY

Multiple myeloma is a neoplastic disorder characterised by the uncontrolled proliferation and accumulation of malignant plasma cells within the bone marrow. Prognosis for myeloma patients is very poor, with median survival of around three years and less than 5% of patients alive at 10 years. Myeloma is associated with high morbidity resulting from anaemia, infections, bone pain and renal failure. Plateau duration is an extremely important clinical end-point as it is associated with low morbidity, few symptoms and better quality of life.

Current standard treatments for myeloma are based on combinations of chemotherapy for all except a sub-set of patients with early stage disease. Because of the lack of progress with conventional chemotherapy regimens, there has been a move towards using higher doses of chemotherapy to combat chemoresistance. The doses of drugs used in high dose chemotherapy (HDC) cause irreversible bone marrow toxicity and require patients to have follow-up blood support with either bone marrow transplantation (BMT) or with peripheral blood stem cell transplantation (PBCT). Due to the high median age of myeloma patients, only around 30% will be eligible for HDC with autologous BMT or PBCT. For patients aged under 55 for whom a suitable donor can be found, allogeneic transplantation is the clinical treatment of choice. There are approximately 2,800 registrations of multiple myeloma in England and Wales each year, approximately 5.5 per 100,000 population per annum (Office of National Statistics - ONS). There were 253 cases of myeloma reported in the Trent Region in 1994.

The Intergroupe Francais du Myelome (IFM) randomised controlled trial reported complete remission rates of 22% and median event-free survival of 27 months in patients treated with HDC and autologous BMT. This compares with only 5% of patients achieving complete remission, and median event-free survival of 18 months in the conventional chemotherapy arm. Improved complete remission rates and improved event-free and overall survival were also reported by smaller phase II studies. The overall survival and EFS benefits based on the results of the IFM trial were both eight months, based on trial data alone. Overall survival benefit for patients under 60 was slightly higher at around nine months.

The estimated cost of HDC procedure for myeloma patients is £12,460, while the estimated standard chemotherapy cost for myeloma patients is £1,980. The cost per life year gained (LYG) for HDC in myeloma is estimated to be £14,970, based on trial data alone. Sensitivity

analysis results indicate that inclusion of five year projected benefits could increase the number of LYG to 1.7, with a cost per LYG of £6,160.

HDC patients tend to have a better quality of life in remission and, thus, require fewer hospital admissions than those treated with conventional chemotherapy. Inclusion of long-term follow-up costs may decrease the marginal cost of HDC. Benefits from HDC will be considerably greater than those reported if quality of life issues are considered. Inclusion of quality of life indices is likely to increase the benefits and reduce the cost per LYG figures based on overall survival only.

# 1. INTRODUCTION

## 1.1 Background to Disease

Multiple myeloma is a neoplastic disorder characterised by the uncontrolled proliferation and accumulation of malignant plasma cells within the bone marrow, and further distinguished by the production of monoclonal immunoglobulin (Ig).

Normally, less than 5% of cells in the normal bone marrow are plasma cells, and these produce immunoglobulins as part of the immune response to infection. Plasma cell numbers are markedly increased in myeloma due to malignant transformation. These are accompanied, in the majority of cases, by excessive Ig production with concurrent suppression of normal antibody production. Morbidity results from the myeloma cell mass and Ig overproduction, leading to anaemia, increased infections, lytic bone disease and renal failure. Quality of life issues are especially important, because, when uncontrolled, the clinical picture is one of recurrent hospital admissions with severe bone pain, infections or fractures, and the need for regular blood transfusions and palliative radiotherapy.

This disease remains incurable with standard chemotherapy; less than 5% of subjects live longer than 10 years.[1] Newer combinations of chemotherapy have also failed to improve true complete remission beyond 5%. Objective responses (partial remission), defined as a reduction in serum or urine protein and marrow plasma cells, can be achieved in 50-60% of subjects with conventional chemotherapy. Unfortunately, median event-free survival or plateau phase and overall survival typically do not exceed 18 and 36 months respectively. Plateau duration, however, is an extremely important clinical endpoint as it is associated with low morbidity, few symptoms and better quality of life.

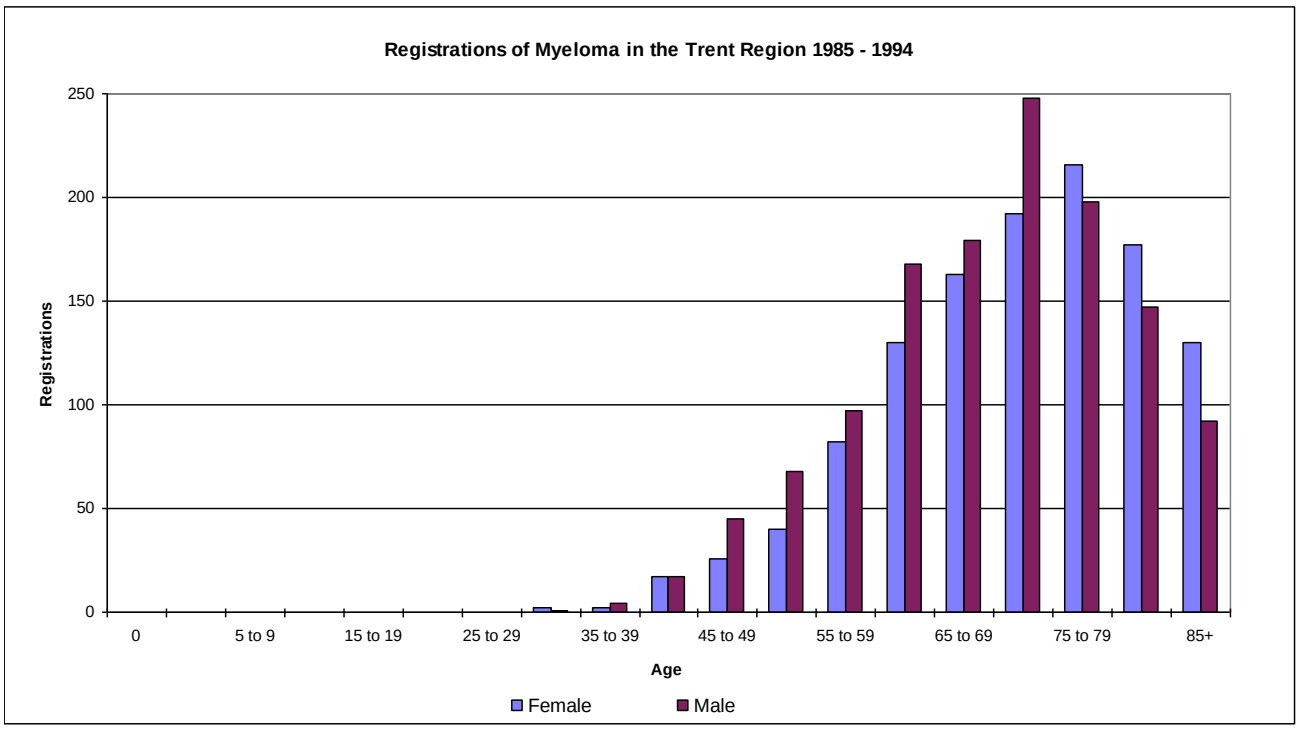
The low incidence of complete remission with conventional therapy suggests marked drug resistance, even in newly diagnosed disease, and has prompted evaluation of dose intensity in attempts to overcome drug resistance in myeloma patients. Transplantation of haemopoietic stem cells (obtained from bone marrow or blood) accelerates restoration of marrow recovery and enables the use of much higher doses of chemotherapy with or without total body irradiation. Such approaches are currently being explored in respect of reported improvements in complete remission rates and event-free and overall survival.[2]

## 1.2 Aetiology and Incidence

The origins of the disease remain unknown. However, the rising incidence in those less than 55 suggests that environmental factors such as radiation exposure, agro-chemical exposure and antigeneic stimulation may have a causative role.[3]

Median age at diagnosis is 70 years, although the incidence in younger subjects is increasing.[3] The disease accounts for 1% of all cancers, though 10-15% of haematological malignancies.[1]

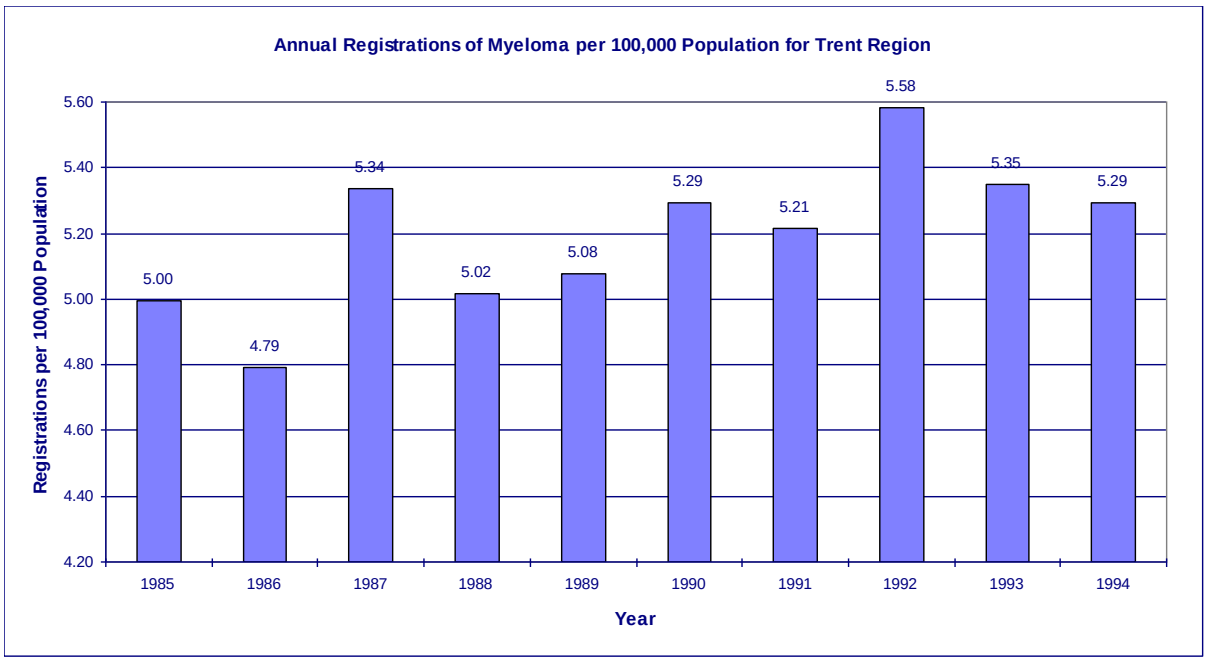
**Figure 1 Trent Age/ Sex Registrations for Myeloma 1985 - 1994**




Source: Trent Cancer Registry

There were 2,810 registrations of multiple myeloma in England and Wales in 1991, with a rate per 100,000 population per annum of 5.8 for males and 5.1 for females.[4] There were 253 cases of myeloma reported in the Trent Region in 1994 (117 male, 136 female). Crude incidence rates for Trent in 1994 were 5 per 100,000 per annum for males and 5.6 per 100,000 per annum for females.[5] (Figure 2 refers).

**Figure 2 Trent Myeloma Incidence Rates 1985 - 1994**




Source: Trent Cancer Registry

## 1.3 Prognosis and Mortality

Careful evaluation of individuals with stratification into low risk, or high risk groups with poorer long-term outcome, is essential. In 1975, Durie and Salmon[6] developed a staging system that is still widely used and divides patients into stage I, II or III on the basis of clinical parameters and myeloma cell mass (i.e. haemoglobin levels, serum calcium, bone disease). The three stages are sub-classified into A or B depending upon the absence or presence of renal failure.

Stage I low cell mass ($<0.6 \times 10^{12}$ cells/$m^2$ )

Stage II intermediate cell mass ($0.6 - 1.2 \times 10^{12}$ cell /$m^2$ )

Stage III high cell mass ( $>1.2 \times 10^{12}$ cells /$m^2$ )

Sub-classification A: serum creatinine value $\geq$ 170 μmol/ l)

B: serum creatinine value $\geq$ 170 μmol/ l)

(Source: International Myeloma Foundation)

Several new prognostic factors have been identified, including $\beta_2$ microglobulin (β2-M), C-reactive protein, and the plasma cell labelling index.[7] At present, no one factor estimates

individual survival consistently. Nonetheless, such evaluations are important, given the wide range of survival.[8] Overall prognosis is poor, with around 50% survival at one year (Tables I and 2). Numbers of myeloma deaths in Trent between 1985 and 1994 are shown in Figure 3.

**Table 1 Median Survival for Multiple Myeloma by Stage**[9]

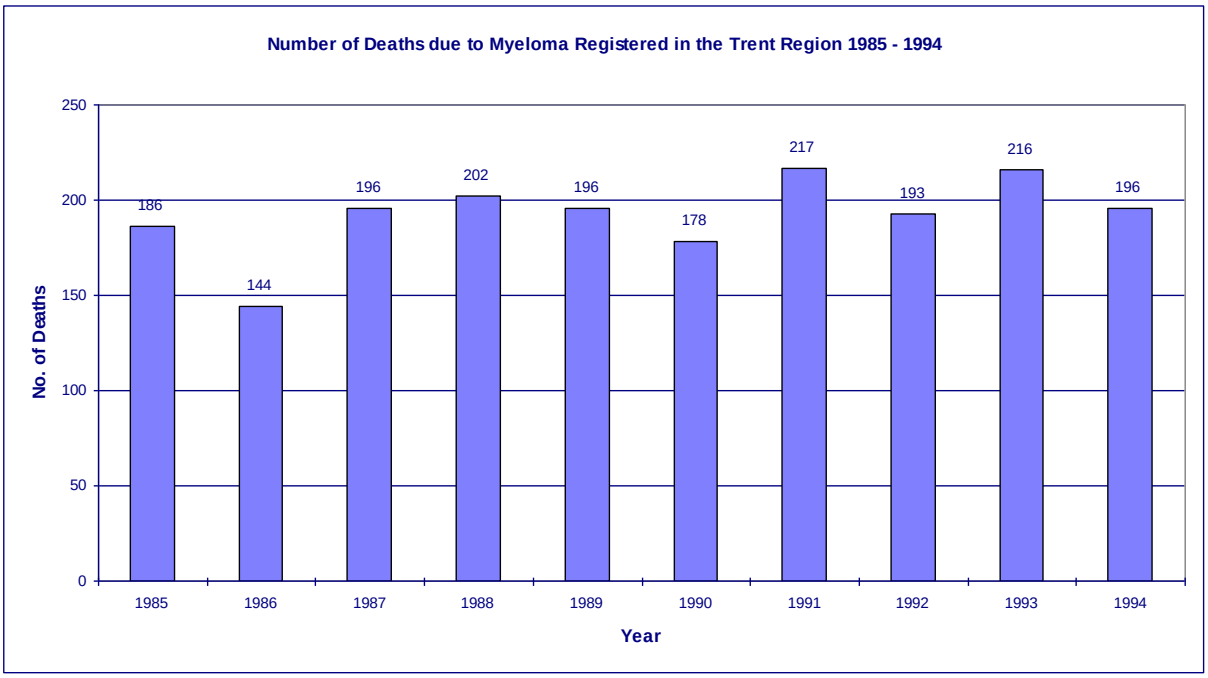
| | |
|---|---|
| Stage I | > 60 months |
| Stage II | 41 months |
| Stage III | 23 months |

**Table 2 Relative Survival Estimates (Based on Cases Newly Diagnosed in 1988)**

| Myeloma | **1 year** | **3 year** | **5 year** |
|---|---|---|---|
| Male | 47% | 24% | 15% |
| Female | 55% | 33% | 24% |

(Source: Trent Cancer Registry)

**Figure 3 Annual Myeloma Deaths in the Trent Region 1985-1994**



## 1.4 Treatment Options

Oral alkylating agents, especially melphalan, and radiotherapy, have been the mainstay of therapy for myeloma, with the exception of indolent disease where close observation is recommended. The introduction of newer combination regimens improve response, but this is not translated into a major survival improvement[10] (Figure 3 refers). Alternative modes of drug administration, particularly continuous infusions of adriamycin and vincristine and pulses of high dose corticosteroids (vincristine/doxorubicin/dexamethasone - VAD, vincristine/adriamycin/methylprednisolone - VAMP) result in higher response rates, up to 20% of cases enter complete remission[11]. Again, responses are not durable, but such therapies produce rapid disease response and do not damage stem cells, enabling autologous marrow collection.

McElwain and Powles[12] demonstrated a dose-response effect *in vivo* using high dose melphalan, with a high response rate (complete remission of up to 35%), but at the price of severe bone marrow depression and significant treatment related mortality (TRM). This prompted the use of high dose chemotherapy (HDC) (with or without total-body irradiation) followed by an infusion by allogeneic or autologous stem cells to rescue patients from the severe haematological toxicity of HDC.[13]

In suitable subjects, initial disease control with combination chemotherapy is followed by stem cell harvest, prior to consolidation therapy with HDC and haemopoietic support. Such therapy has a high response rate, with improved quality of life and a median overall survival of 4 to 5 years.[14]

## 1.5 Scale of Problem in a 'Typical' District

In a 'typical' district of 500,000 people, approximately 27 newly reported cases of multiple myeloma would be expected each year. Myeloma accounts for around 200 deaths in the Trent Region per annum (Office of National Statistics - ONS).

In order to treat all eligible patients with HDC, the additional costs to a 'typical' health authority of HDC over initial conventional chemotherapy costs would be around £120,000 per annum. Current practice suggests over half of eligible patients are already receiving HDC and, thus, the extra costs required would be around £60,000. However, in some health authorities a smaller proportion of eligible patients is being treated with HDC. (See Section 3 for more detailed discussion of likely costs).

### 1.6 European Blood and Marrow Transplant Registry

The European Blood and Marrow Transplant Registry (EBMT) is a collaborative group established in the 1980s. The aims of the EBMT include:

- Collection of clinical data on patients undergoing HDC;
- Sponsorship of large clinical trials in HDC;
- Development of minimum standards and accreditation guidelines for HDC.

The EBMT includes a number of sub-groups with responsibility for the major tumour types commonly treated with HDC, e.g. lymphoma, solid tumours, leukaemias, paediatric malignancies etc.

In the UK, a subsidiary group, The British Society for Blood and Marrow Transplantation (BSBMT) has recently been established. Membership of the EBMT and BSBMT is voluntary. There is no obligation on clinicians to register their data with these organisations. However, there is a general consensus that, given the morbidity, mortality and cost implications of these treatments, patients not in clinical trials should have their data recorded. Data from the EBMT for 1996 are now available and show the commonest uses of HDC.

EBMT guidelines advocate allogeneic bone marrow transplantation (alloBMT) in multiple myeloma preferably in patients up to the age of 55 who have responded to first-line treatment, or before second-line treatment in subjects resistant to first-line treatment. Allogeneic transplantation with sibling donors may be considered for selected patients. Transplantation with unrelated donors should only be considered on a 'developmental' basis. Autologous transplantation (ABMT) is an option for patients below 65 years of age

who respond to first-line treatment. These guidelines are currently in draft form, but are generally endorsed and are likely to be accepted.

**Table 3 HDC Notifications from EBMT Data in 1996**

| Disease | Notifications |
|---|---|
| Non-Hodgkin's Lymphoma (NHL) | 2,645 |
| Breast Cancer | 2,156 |
| Acute Myeloid Leukaemia (AML) | 1,878 |
| **Myeloma** | **1,856** |
| Chronic Myeloid Leukaemia (CML) | 1,382 |
| Acute Lymphoblastic Leukaemia (ALL) | 1,275 |
| Hodgkin's disease | 739 |

**Table 4 EBMT Proposed Classification of Transplant Procedures for Myeloma - 1998**

| | EBMT DRAFT RECOMMENDATIONS | | | | Local Clinical Interpretation |
|---|---|---|---|---|---|
| **Disease** | **Status** | **Allogeneic - Sibling** | **Allogeneic - Unrelated** | **Autologous** | **Autologous** |
| *Myeloma* | Stage I | CRP | NR | CRP | CRP |
| | Other | CRP | D | R | R |

**CRP** To be undertaken in approved Clinical Research Protocols

**D** Developmental

**R** In routine use for selected patients

**NR** Not generally recommended

## 2. THE USE OF HIGH DOSE CHEMOTHERAPY IN THE TREATMENT OF MULTIPLE MYELOMA: SUMMARY OF EVIDENCE OF EFFECTIVENESS

### 2.1 Introduction to Treatment in Multiple Myeloma

Conventional chemotherapy cures few, if any, patients (Figure 4 refers).

**Figure 4 Overall Survival Results with Conventional Chemotherapy**

*Source: Alexanian and Dimopoulos (1994)*[10]

**N.B. The graph uses a logarithmic scale for survival**

This failure of standard chemotherapy, together with demonstrations of a dose-dependent response to chemotherapy provide the rationale for HDC. Extensive phase II studies with myeloablative therapy followed by stem cell rescue, support the notion that 'more is better', effecting complete remission rates of 40-50% with event-free survival and overall survival of the order of three and five years respectively, when performed early in the disease. Patients achieving a complete remission had an absence of bone pain with markedly improved performance status and quality of life.[13,15]

On the basis of this evidence, HDC is becoming standard treatment for a select group of patients. There is currently regional variation regarding the use of HDC, with specialist centres often treating patients with HDC and District General Hospitals entering patients into the ongoing Medical Research Council (MRC) trial. Only around 30% of all myeloma patients will be eligible for HDC, of whom around 50% within the Trent region will be currently receiving the treatment. This would result in around 5-10 patients per annum for a 'typical' district within Trent.

## 2.2 Treatment Eligibility

Autologous transplantation has been offered to patients up to 70 years of age, but is associated with a higher treatment related mortality over 60. Given the high median age of patients with multiple myeloma, it is estimated that only around 30% are suitable for HDC.

Allogeneic bone marrow transplantation (alloBMT) can only be applied to young patients, usually under 50, with human leukocyte antigen (HLA) -identical siblings. It also carries a risk of graft-versus-host disease.[16] Consequently, it is currently limited to about 5% of cases and most receive autologous transplants following HDC.

## 2.3 Autologous Versus Allogeneic Transplantation

AlloBMT offers the advantage of a lack of tumour cell contamination and a graft-versus-myeloma effect.[17] The major problem with alloBMT has been the very high treatment related mortality. While alloBMT results in a lower relapse rate than autografting, treatment related mortality following an allograft is much higher (13% with autologous compared with 41% with allogeneic). Consequently, in a pair-mate analysis with 63 autotransplants, overall survival was superior in the autotransplant group.[18] Recent studies suggest decreased

procedural mortality and better survival if transplantation is undertaken early (40% versus 20%).[19,20] Newer lower intensity allograft procedures may also reduce TRM.[21]

## 2.4 Survival following Allogeneic Transplant

Importantly, the survival curve in alloBMT beyond five years approaches a plateau (compare with figure 4), and alloBMT is probably the only genuinely curative approach in myeloma at present. As such, it is argued that this approach should be considered in preference to an autologous procedure in newly diagnosed myeloma patients under 50 years of age.

**Figure 5 Overall Survival Results with Allogeneic Transplant**

This study involved a heterogeneous group of myeloma patients. Survival is reported as time after BMT, which could be several months post-diagnosis.

**MULTICENTRE EBMT REGISTRY STUDY**

*Source: Gahrton et al. (1991)[22]*

## 2.5 Assessment of Trial Results

### 2.5.1 Single Autologous Transplantation

Several uncontrolled studies of HDC followed by autologous marrow or peripheral blood stem cell transplantation (PBCT) have been reported. Collectively, these show highly encouraging increased remission and survival rates, with low treatment related mortality and improved quality of life.[13,23] These findings have been confirmed by a recent prospective randomised trial.[14] This is the only randomised controlled trial (RCT) for the use of HDC with BMT for myeloma patients.

### 2.5.2 Randomised Studies

***Attal et al. (1996) - Intergroupe Francais du Myelome (IFM) - study of ABMT Versus HDC in Myeloma***.[14]

200 newly diagnosed patients, aged under 65, with stage II/III multiple myeloma were randomised to receive either vincristine/melphalan/cyclophosphamide/prednisolone or vincristine/carmustine/dexorubicin/prednisolone (VMCP/BVAP) combination chemotherapy for 12 months, or HDC which consisted of 4-6 cycles of VMCP/BVAP followed by an autograft (ABMT).

Analysis on an intention to treat basis showed that HDC resulted in significantly superior complete remission (22% versus 5%), as well as projected five year event-free survival (28% versus 10%) and overall survival (52% versus 12%) as compared with standard therapy (Table 5). Treatment-related mortality was similar. Median follow-up was 37 months in the conventional arm and 41 months in the HDC arm.

**Table 5 Survival and Remission Rates for IFM Randomised Trial**

| Outcome | Conventional Chemotherapy | High Dose Therapy & ABMT | p-value |
|---|---|---|---|
| Median EFS | 18 months | 27 months | |
| Median OS | 37 months | not yet reached | |
| 5 year event-free survival | 10% | 28% | p=0.01 |
| 5 year overall survival | 12% | 52% | p=0.03 |
| Complete remission | 5% | 22% | |
| Very good partial response | 9% | 16% | |
| Progressive disease | 25% | 12% | |

Benefits of HDC were most marked in patients under 60 years of age, with 70% probability of five year overall survival compared to 18% for conventional therapy. However, only 58% of those over 60 completed intensive treatment. There was no significant survival advantage for HDC in patients over 60.[24]

This trial appears to provide the strongest evidence to date for HDC in patients aged 60 and under.

## 2.6 Ongoing Trials

Further randomised studies are currently in progress in the UK (MRC Myeloma VII) and in the USA (US Intergroup Study). MRC Myeloma VII is the largest study to date, where newly diagnosed subjects with myeloma, under 65 years of age, are randomly assigned to conventional therapy or HDC with autologous stem cell support. Cost-effectiveness and quality of life issues are also being addressed. Recruitment problems have been encountered by the MRC due to early reporting of results of the IFM trial,[14] which led many centres to consider the case sufficiently proven. As such, it is difficult to know when the trial will report.

The US Intergroup study has recently been modified in the light of the IFM results, however, with the previously optional PBSC collection after induction therapy now mandatory. Hence, the objective of this study is now whether an early transplant is superior to salvage therapy.

### 2.6.1 Non-randomised Studies

Several non-randomised studies of newly diagnosed patients receiving conventional chemotherapy followed by HDC and an autograft have been reported (Table 6 refers). Collectively, these demonstrate that complete remission rates increase from about 5% with standard therapy to about 40% with myeloablative therapy, and overall survival varied between 2.7 and 6.7 years. Treatment related mortality is low (2% to 11%). These studies confirm the efficacy and safety of HDC with autologous stem cell transplantation. Thus far, no study has shown that conventional therapy is better, and overall survival is consistently higher than the median survival of around 2 - 2.5 years using conventional chemotherapy (see Figure 4).

**Table 6 Phase II Studies of HDC in the Treatment of Multiple Myeloma**

| Author | Patient Nos. | Median Age (Years) | Follow-up (Years) | Complete Remission (%) | Median Event-Free Survival (Years) | Median Overall Survival (Years) |
|---|---|---|---|---|---|---|
| Cunningham, 1994[25] | 53 | 52 | 2.6 | 75% | 2 | 6.7 |
| Anderson, 1993[26] | 52 | 49 | NA | 40% | 2.6 | 4.2 |
| Bjorkstrand, 1995[27] | 207 | 49 | NA | 46% | 2.4 | 2.7 |
| Harousseau, 1995[23] | 133 | 52 | 3 | 37% | 2 | 3.8 |
| Fermand, 1995[28] | 63 | 44 | 7.5 | 20% | 3.6 | 6.4 |
| Powles, 1997[29] | 112 | NA | NA | 53% | 2.3 | 6.6 |
| Jagannath, 1996[30] | 231 | 51 | 3 | 37% | 3.6 | 5.2 |

NA-not available

## 2.7 Double Autologous Transplantation

Despite increased complete remission rates and improved prognosis, disease relapse remains a problem and a double autograft procedure has been used as an alternative strategy to intensify treatment.[11] Two retrospective analyses, conducted exploring tandem transplants, have shown an increase in rates of partial and complete remission.

### 2.7.1 Double Transplantation Versus Conventional Chemotherapy.

***Barlogie et al., 1997: Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma.***[11]

In a pair-mate analysis, the outcome of 123 patients under 70 years of age with symptomatic multiple myeloma receiving 'total therapy' was compared to that of patients in the Southwest Oncology Group (SWOG) treated with standard therapy. Total therapy consisted of VAD induction chemotherapy, followed by a stem cell harvest, further combination chemotherapy and then high dose melphalan with stem cell rescue. Three to six months later, responding patients received a second autograft. 76% of patients completed total therapy, with a 4% treatment-related mortality in the first year.

116 pair-mates, matched for age, creatinine and $\beta_2$M, were selected from both total therapy and 1,123 SWOG patients. As in the IFM randomised study, total therapy, analysed on an intention to treat basis, was superior to standard therapy, with a higher partial remission rate (85% compared with 52%), longer median event-free survival (49 versus 20 months, p=.0001) and overall survival (62+ versus 46 months, P=.003). Of patients completing two autografts, 48% achieved a complete remission.

***Vesole et al., 1996: Double autotransplants in myeloma.***[31]

This analysis of 496 subjects, from a single centre, enrolled into clinical trials of double transplantation, demonstrated that this approach was feasible up to 70 years of age. 363 patients (73%) completed the second transplant. The complete remission rate increased from 24% to 43% following the second transplant, while the non-response rate fell from 32% to 19%. Regardless of pre-transplant biological factors, median overall survival exceeded 5.5 years where transplantation was undertaken within 12 months of diagnosis and the second procedure followed within six months of the first.

### 2.7.2 Double Versus Single Transplantation

This apparently greater cytoreduction has prompted an IFM randomised trial comparing one versus two transplants. Early analysis of 200 patients shows a complete remission of 32% with 74% overall survival at two years (Attal et al., unpublished), but no clear difference, at present, between the groups. Clearly, the impact of such aggressive strategy needs further evaluation.

## 2.8 When to Transplant

The optimal timing of autologous transplantation remains to be determined. Transplantation was performed as part of initial therapy in the IFM study.[14] Whether delayed autograft, at the time of disease progression, is also of benefit, requires further clarification by ongoing trials, such as the US Intergroup study.

French investigators have randomised 185 patients to receive HDC and PBCT either early, or late, as a salvage strategy following relapse after VAMP chemotherapy.[24] Preliminary

results suggest an equivalent outcome in terms of overall survival, but early HDC was associated with a longer period of treatment, suggesting a clinical benefit for this approach. Median event-free survival was 39 months with an estimated overall survival of 58 months.

Results of uncontrolled studies indicate that autologous transplantation is a useful salvage therapy for primary refractory disease, although of limited value in resistant relapse.[31]

## 2.9 Source of Autologous Stem Cells

Autologous stem cells can be obtained from both autologous bone marrow transplantation and peripheral blood stem cell transplantation. The source of autologous stem cells had no significant impact on long-term results.[23] PBCT is currently preferred, however, because of more rapid haemopoietic recovery. Furthermore, peripheral blood stem cell harvests can be performed on an out-patient basis, avoiding the morbidity of anaesthesia and marrow harvesting. The speed and degree of haematopoietic engraftment is related to the duration of prior therapy and is readily predicted by the quantity of CD 34 stem cells mobilised.[32]

Contamination of the autologous graft remains a concern, with clonal B cells present in both sources of autograft.[33] This has led to attempts to reduce such tumour cells either by negative purging or by the use of positive selection based on CD 34 antigen expression.[34] CD 34-selection does reduce the level of contamination in the reinfused product, but it is not yet known whether this leads to a lower relapse risk. Randomised studies addressing this issue are in progress.

## 2.10 Summary

Multiple myeloma, when uncontrolled, is characterised by frequent hospital admissions with severe bone pain, fractures, and infections. This, together with the requirement for blood product support and palliative radiotherapy, results in a poor quality of life for many patients. Conventional chemotherapy has failed thus far to make major inroads into disease outcome. Some progress has, at last, been achieved by a 'more is better' approach. For many, conventional chemotherapy is still the only possibility; however, high dose therapy with stem cell support is feasible in about 30% of cases and undoubtedly produces a more dramatic anti-myeloma effect with a better quality of remission.

The role of HDC in the first-line treatment of patients with multiple myeloma appears well established with the Attal[14] randomised trial providing clear overall and event-free survival advantages. The role of HDC as a double transplant procedure may potentially provide even greater patient benefit. However, this remains to be proven by randomised trial.

Analysis of the current data indicates that HDC with haemopoietic support, when compared to conventional treatment, shows:

- increased survival (52% vs 12% at 5 years; p=0.03);[14]
- increased plateau duration (28% vs 10% at 5 years, p=0.01);[14]
- improved performance status and quality of life;[13,15]
- low treatment-related mortality.[3,14]

The indications are that this treatment should be introduced early in the course of the disease.

# 3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

## 3.1 General

This economic analysis is based on RCT data using single transplantation following HDC. The principal trial on which it is based is the IFM[14] which gives outcomes of both overall survival and event-free survival at 15, 30, 45 and 60 months. Using these data, the benefits have been estimated in terms of overall survival and progression-free survival comparing conventional chemotherapy with HDC supported by transplant.

Area under the curve techniques have been used to estimate clinical benefit. This approach has a number of advantages:

- it allows the experience of the whole cohort to be considered;
- it removes the potential bias of median point estimates (as relative risk can change over time);
- median point outcomes are not always achieved during the trial period;
- median point estimates considerably underestimate the benefits in treatments which have high initial mortality, but in which survival curves later reach a plateau. (See Figure 5).

### 3.1.1 Benefits of Single Transplantation Following HDC in Multiple Myeloma

Using these curve estimates, it is predicted that the marginal event-free survival benefit of HDC over standard chemotherapy in the treatment of multiple myeloma is approximately eight months (32 months c.f. 24 months).

This estimate is taken as the difference between the area under the curve up to the end of the trial results, in this case 60 months. This may undervalue gains, as any benefit of the HDC arm is assumed to cease at the end of the trial period.

Similar estimates have been made for overall survival, for all patients and also for patients aged 60 and under.

**Figure 6 Attal IFM study[14] - Event-free Survival Curve - All Patients**

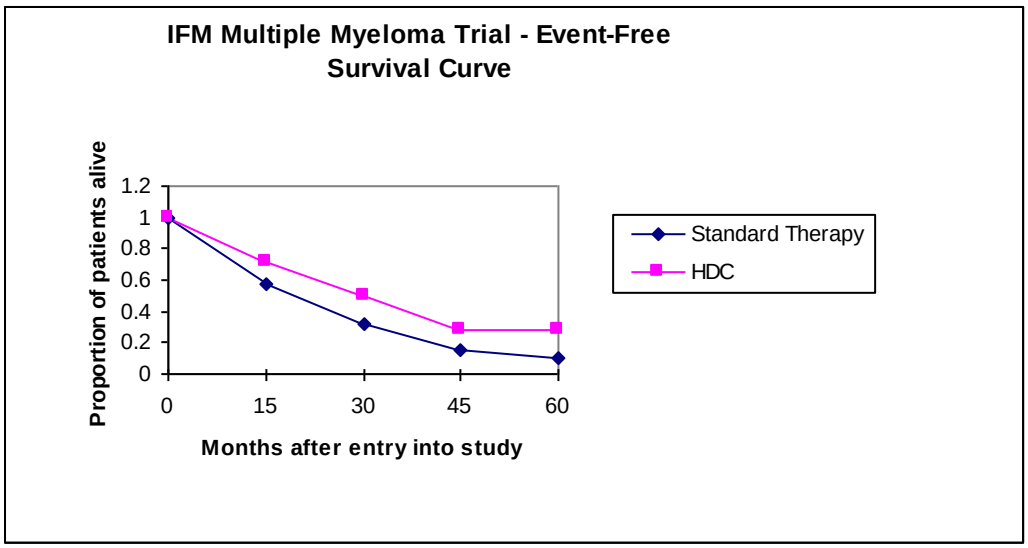
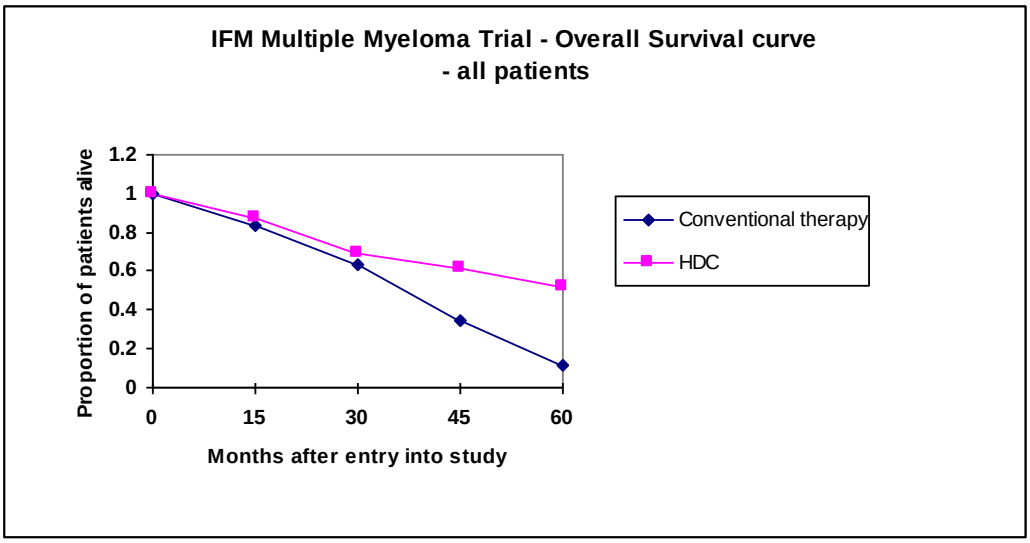
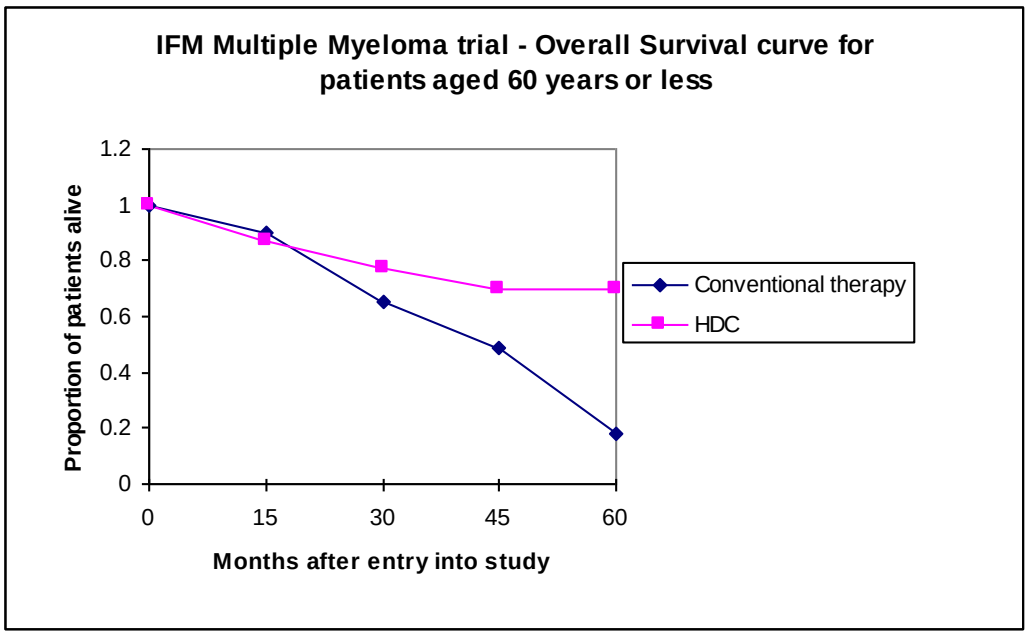



**Figure 7 Attal IFM Study - Overall Survival Curve - All Patients**




Using these curve estimates, it is predicted that the marginal overall survival benefit of HDC over standard chemotherapy is approximately eight months (44 months c.f. 36 months). Again, the additional benefits of HDC are assumed to cease at the end of the trial period.

**Figure 8 Attal IFM Study - Overall Survival Curve- Patients <60 Years of Age**




In patients aged 60 years and under, the marginal overall survival benefit of HDC over standard chemotherapy is approximately nine months (48 cf. 39 months).

### 3.1.2. Benefits of HDC in Terms of Quality of Life

These benefit analyses consider only the years of life and years of event-free survival gained; they make no allowance for the improved quality of life experienced by those receiving HDC. Quality of life issues, although difficult to quantify, are important because when uncontrolled, the clinical picture is one of recurrent hospital admissions with bone pain, fractures or infections.

Although it is generally recognised that patients who respond to HDC tend to have a better quality of life than those patients treated with conventional chemotherapy, there is little published evidence quantifying these benefits in terms of quality of life. Small studies have reported improved quality of life for patients receiving HDC, with over two years excellent quality life years gained and a return to normal life and work for a proportion of the patients.[15] This improvement in quality of life is reflected in local autologous transplant patients, of whom around 50% returned to work.

Quality of life measures have not been considered by trials reported to date, but will be included within the MRC trial. However, this trial is currently still recruiting and data will not be available for a number of years.

## 3.2 Treatment Costs for Multiple Myeloma

### 3.2.1 Cost of HDC Therapy for Multiple Myeloma

Information on the relative cost of treatment for myeloma has been provided by the finance department at Central Sheffield University Hospitals NHS Trust. The main areas of difference between standard chemotherapy and HDC are the need for a harvesting procedure and the requirement for in-patient care for the latter.

The contract costs for the HDC are based on pre-HDC chemotherapy estimated at £990, a 3-4 week in-patient stay in a haematology ward, estimated at £8,420, plus six day visits at £200 per day and additional drug costs of £1,850. This results in a total cost for the high dose procedure of £12,460.

The costs of the standard chemotherapy regimen for the patients who may be considered for treatment with HDC are estimated at between £1,980 and £2,970. This is based upon a regimen of six to nine courses of chemotherapy at £130 per course (£100 chemotherapy drugs and £30 anti-sickness drugs), with an additional day-case cost of £200 per course. Not included are any in-patient costs, such as admissions with infection or any orthopaedic procedures, incurred during standard therapy.

These costs are for initial therapy only, and, therefore, likely to be underestimates. Significant other costs such as blood transfusions, orthopaedic admissions, radiotherapy, and analgesia are not included. These may well be lower for patients undergoing HDC, as the HDC procedure is followed by longer symptom-free periods and improved performance status.

### 3.2.2 Long-term resource use for myeloma patients

There is very little evidence available quantifying long-term resource use for myeloma patients. The only available published study considering cost-effectiveness of HDC for myeloma is reported by Henon et al.,[15] comparing costs and outcomes of 12 patients with

Grade III myeloma treated with HDC and PBCT with 10 similar patients undergoing conventional chemotherapy. Eight of the 10 patients undergoing conventional chemotherapy died within one year of initial chemotherapy (range 3-12 months). During this time they were discharged from hospital for short periods only and their average cumulative hospitalisation was 4.8 months. The remaining two patients died of relapse two and four years from initial chemotherapy. Patients undergoing HDC with PBCT stayed in hospital for a median time of 28 days from the start of conditioning. One patient died of procedure-related toxicity and eight others achieved complete remission, of whom two died of unrelated causes. Four were still in unmaintained complete remission with a median follow-up of four years.

This study does not consider adequate numbers to provide cost estimates, but does demonstrate the difference in resource use for the two groups, with the conventional chemotherapy patients gaining little in terms of reasonable quality life.

Ideally, it would be possible to quantify these ongoing costs via primary research of patient records and Patient Information System (PIS) data, comparing resource usage for patients undergoing HDC with those receiving conventional chemotherapy. Although it was possible to examine a small number of patient records, a complete analysis of lifetime costs of each group is not realistically possible for several reasons:

- records are not available for patients who have died;
- of the 10 autologous transplants which have taken place within Central Sheffield University Hospitals NHS Trust since 1989, five were in the past year and, thus, have no long-term follow-up available;
- an accurate picture of typical resource use would need a larger volume of records as patient requirements vary significantly.

PIS data were also unable to provide clear information regarding the ongoing hospital resource use for myeloma patients:

- the secondary diagnosis code of myeloma is frequently omitted for orthopaedic admissions;
- long-term follow-up would require analysis of several years' data;
- it is difficult to differentiate between patients undergoing HDC and those receiving standard chemotherapy from the procedure codes used.

Consideration of long-term follow-up costs is likely to reduce the marginal cost of treatment for HDC, as patients treated with HDC will cost less to support than those receiving conventional chemotherapy. Due to the paucity of data available, it has not been possible to quantify the differences in resource use for the two treatment groups. However, the reduced marginal difference will result in a lower cost per life year gained (LYG).

If quality of life issues are included, the cost-effectiveness of HDC will improve considerably as HDC patients will typically have a longer period in remission during which they will benefit from excellent quality of life and return to previous working status. Clinical opinion suggests that the incorporation of quality of life values into economic analyses will increase the benefit of HDC and provide a quality adjusted cost per LYG estimate which is considerably lower than that suggested by the trial data alone.

Therefore, the most that can currently be said on the basis of clinical observation and the results of reported case series is that it is likely that, after transplantation, HDC patients will cost less to support than conventional patients. However, it is important to stress that, even without these costs included, the economic argument for HDC is a positive one.

### 3.3 Cost-effectiveness of High Dose Chemotherapy for Multiple Myeloma

In considering the cost-effectiveness of HDC in multiple myeloma, the overall survival benefits for all patients (as discussed in Section 3.1) are compared with the implied marginal costs. The marginal survival benefit, as derived from the trial alone, is shown in Table 7, while the projected one and five year benefits derived from long-term follow-up data are considered in the sensitivity analysis.

**Table 7 Cost-effectiveness of HDC in Multiple Myeloma: Trial Based Data**

| Cost-Effectiveness Based on Trial Data Only (60 Months) | Standard Chemotherapy | High Dose Chemotherapy | Marginal Survival Analysis |
|---|---|---|---|
| Therapy cost | £1,980 | £12,460 | £10,480 |
| Survival (area under the curve estimate) | 36 months | 44 months | 8 months |
| | 3.0 LYG | 3.7 LYG | 0.7 LYG |
| Marginal cost per LYG | - | - | £14,970 |

Based on this analysis, the marginal survival benefit of HDC is predicted to be 0.7 years and the increase in treatment cost to be £10,480. This translates into a cost of £14,970 per LYG.

### 3.4. Sensitivity Analyses

#### 3.4.1. Long-term Projected Benefits

The above estimates consider benefits accrued during the five year trial period only. However, there may be further potential long-term gains for some patients receiving HDC when compared to standard therapy.

At present there are no randomised trial data which quantitate such long-term outcomes. Non-randomised follow-up data from a single centre study reported by Cunningham, et al. (1994)[25] have been examined, therefore, to estimate these putative long-term benefits. The outcomes in this study were comparable to those of the IFM trial (five year survival quoted at 15% for conventional chemotherapy and 45% for HDC).

The results were reported at six years[13] and 10 years.[29] The most pessimistic scenario for one year follow-up is that the conventional arm retains the same benefits at six years as at five, and overall survival for the HDC is equivalent to that reported by Cunningham et al.[25]

In order to calculate potential benefits at 10 years, an assumption has been made of a 5% 10 year survival with conventional therapy[31] and 15% survival at 10 years for the HDC arm as reported by Powles et al.[29]

Attempts to produce similar estimates for event-free survival at 10 years are limited by the fact that disease progression will have occurred in most, if not all, patients receiving both conventional chemotherapy and HDC.

Consideration is given to the additional potential benefits based upon non-randomised trial results at one year and five year follow-up data; the marginal survival benefits increase and further reduce the estimated cost per LYG.

**Figure 9 One Year Projected Survival Benefits of HDC over Standard Chemotherapy**

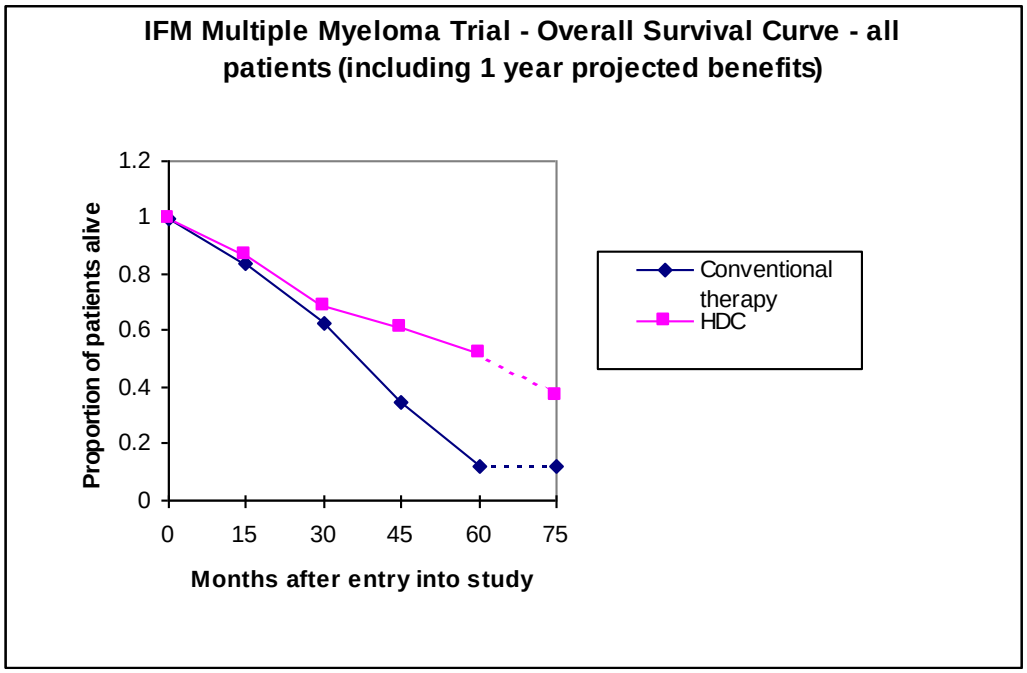


**Figure 10** **Five Year Projected Survival Benefits of HDC over Standard Chemotherapy**

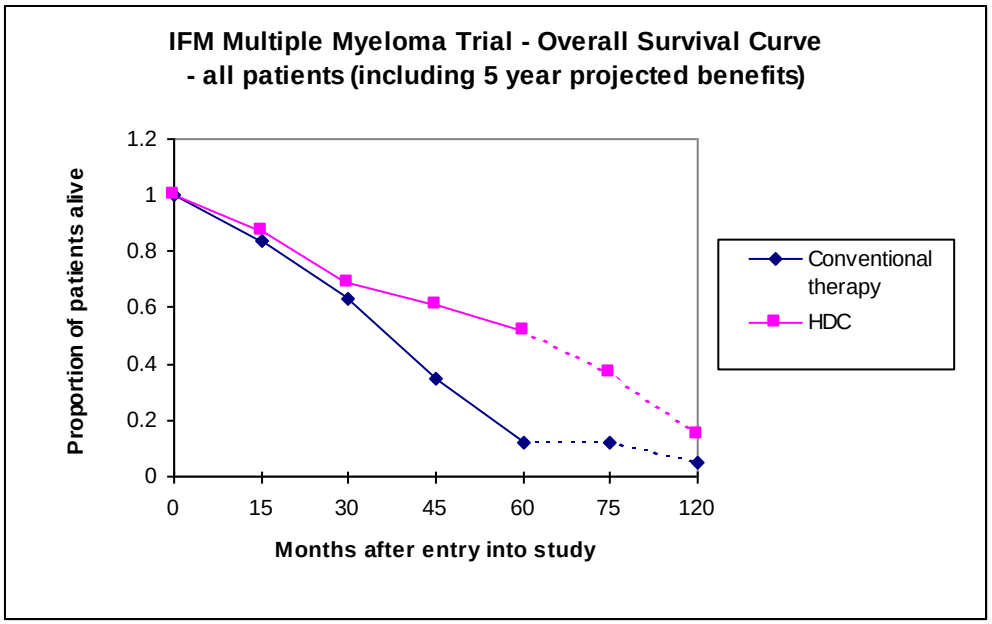



**Table 8** **Comparative Survival Benefits from the Cunningham[25] Study**

| Forward Projection of End of Trial Benefits | Survival Benefit (Months) | LYG |
|---|---|---|
| 1 year | 11 (48 cf. 37 months) | 0.9 |
| 5 year | 20 (60 cf. 40 months) | 1.7 |

**Table 9** **Cost-effectiveness of High Dose Chemotherapy in Multiple Myeloma: Extended 1 Year Benefits Assumed**

| Cost-effectiveness Including One Year Projected Benefits | Standard Chemotherapy | High Dose Chemotherapy | Marginal Survival Analysis |
|---|---|---|---|
| Therapy cost | £1,980 | £12,460 | £10,480 |
| Survival (Area Under the Curve estimate) | 37 months | 48 months | 11 months |

| | | | |
|---|---|---|---|
| | 3.1 LYG | 4.0 LYG | 0.9 LYG |
| Marginal cost per LYG | - | - | £11,640 |

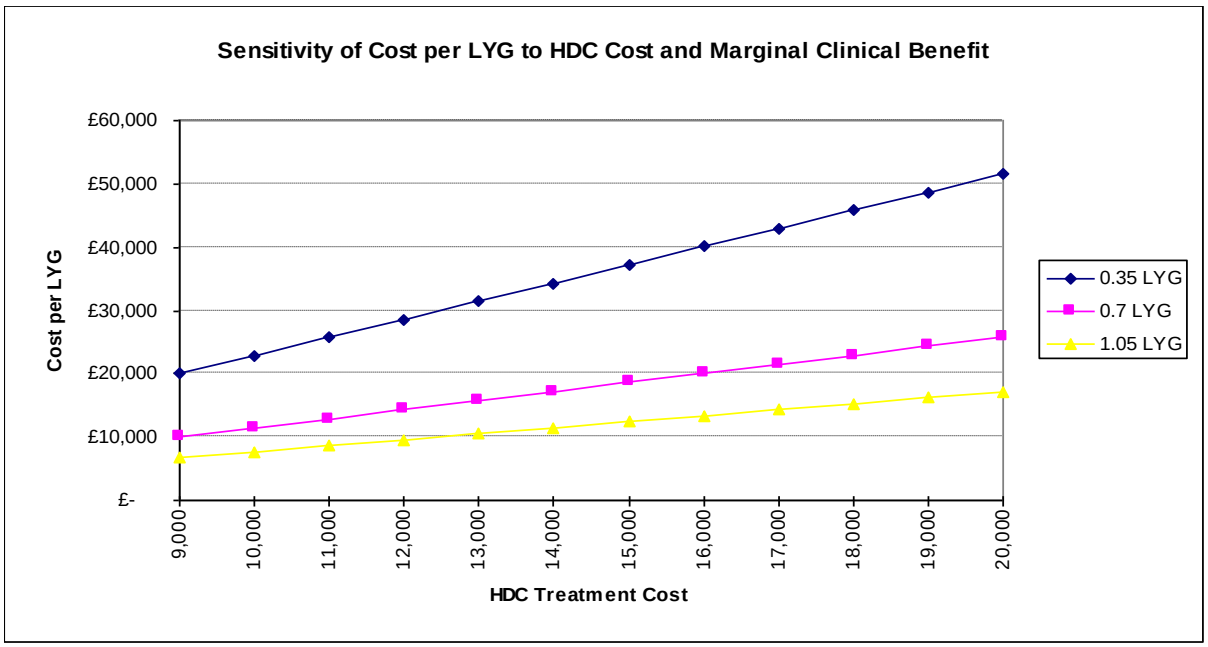
**Table 10 Cost-effectiveness of High Dose Chemotherapy in Multiple Myeloma: Extended 5 Year Benefits Assumed.**

| **Cost-effectiveness Including Five Year Projected Benefits** | **Standard Chemotherapy** | **High Dose Chemotherapy** | **Marginal Survival Analysis** |
|---|---|---|---|
| Therapy cost | £1,980 | £12,460 | £10,480 |
| Survival (area under the curve estimate) | 40 months | 60 months | 20 months |
| | 3.3 LYG | 5.0 LYG | 1.7 LYG |
| Marginal Cost per LYG | - | - | £6,160 |

3.4.2 Sensitivity of Cost Per Life Year Gained to Costs of HDC and Marginal Clinical Benefits

The following sensitivity analyses are based upon the results reported during the IFM trial only. To examine 'best' and 'worst' case scenarios, costs for HDC ranging from £9,000 (the basic HDC cost without additional drug costs) to £20,000 have been explored. The effects of a reduction in clinical benefits to only half those reported in the trial have also been considered.

**Figure 11 Sensitivity of Cost per LYG in Multiple Myeloma**




- Even with the cost of HDC increased to £20,000, the cost per LYG does not exceed £25,000.
- Assuming the clinical benefits to be 50% lower than those reported in the trial, the cost per LYG increases to around £37,000.

## 4. OPTIONS FOR PURCHASERS AND PROVIDERS

High Dose Chemotherapy is feasible in about 30% of patients with multiple myeloma. Such therapy increases remission rates, improves event-free survival and overall survival and results in improved quality of life. At present randomised controlled trial data, indicating a benefit for single transplantation, are available from a single trial, whilst the role of double transplant procedures is under investigation.

The options for purchasers can be summarised as follows:

**Single transplantation**

1. Purchase conventional chemotherapy until the MRC trial reports (N.B. this would accentuate recruitment problems already experienced by the MRC trial and would delay reporting);
2. Enrol suitable patients into the MRC trial;
3. Purchase HDC for suitable patients:
    - allogeneic transplant for those aged <50 with HLA-identical sibling donor;
    - autologous transplant for those with a health status equivalent to, or better than, an average 65 year old, with good performance status, stage II/III disease.
4. Purchase HDC for all myeloma patients (this is currently not justified with no benefit shown for older patients).

## 5. DISCUSSION AND CONCLUSIONS

Due to the small number of patients involved, the evidence for the use of HDC in myeloma patients is based around one randomised trial and several small observational studies. These clearly indicate benefits in terms of survival, event-free survival and improved quality of life for a sub-set of myeloma patients.

HDC has already been accepted by some as standard treatment, but there are trials ongoing to quantify further the benefits and explore options for further treatment, i.e. the use of double transplants.

Draft EBMT guidelines recommend autologous transplantation for patients under 65 years of age who respond to first-line treatment for stages II and III. Allogeneic transplantation has been recommended for patients who respond to first-line treatment or before second-line treatment for patients who do not respond to first-line treatment. Allogeneic transplantation is only recommended in the EBMT guidelines for patients up to the age of 55 for whom a suitable donor can be found.

There is an Health Technology Assessment (HTA) report in progress which considers the evidence for HDC in a range of cancers, including a short section on myeloma. At the time of writing this report, the HTA report was in the process of publication. However, a summary of its draft conclusions has been made available to the authors.

These draft conclusions recommend participation in trials[14,28] as they do not consider it possible at this stage to comment reliably on the efficacy of HDC with autologous transplantation. However, the basis for their reservations on the use of HDC in myeloma is not explained, although it is likely to be because only a single randomised trial is available. Allogeneic transplantations are considered an experimental therapy.

## 6. USE OF HIGH DOSE CHEMOTHERAPY IN THE TREATMENT OF MULTIPLE MYELOMA: SUMMARY MATRIX

| PATIENT GROUP | PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS) | ESTIMATED FUTURE ACTIVITY | OPPORTUNITY FOR COST SAVING | AUDIT POINTS | EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT | COST-EFFECTIVENESS |
|---|---|---|---|---|---|---|
| Newly diagnosed multiple myeloma patients. | Patients who have a health status equivalent to, or better than, an average 65 year old. | Expected 10 cases per annum for 'typical' district of 500,000 pop. | Reductions in hospital admissions, blood transfusions, analgesia, palliative radiotherapy etc. | Overall survival, event-free survival. | Increased event-free survival and overall survival, potential of achieving cure.<br><br>Projected 0.7 LYG per patient (minimum) | Marginal cost per LYG of initial treatment of £14,970 |

## REFERENCES


1 Handelsman H. Haematopoietic stem-cell transplantation in multiple myeloma. *Cancer Treat Rev* 1996; 22: 119-125.

2 Blade J, San Miguel JF, Fontanillas M, et al. Survival of multiple myeloma patients who are potential candidates for early High-Dose Therapy intensification/Autotransplantation and who were conventionally treated. *J Clin Oncol* 1996; 14: 2167-2173.

3 Varterasian ML. Biologic and clinical advances in multiple myeloma. *Oncology* 1995; 417-424.

4 Cancer Registrations. HMSO; 1999.

5 Trent Cancer Registry, Weston Park Hospital, Sheffield. 1998.

6 Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. *Cancer* 1975; 842-854.

7 Greipp PR. Prognosis in myeloma. *Mayo Clin Proc* 1994; 69: 895-902.

8 MacLennan ICM, Chapman C, Dunn J, et al. Combined chemotherapy with ABCM versus melphalan for treatment of myelomatosis. *Lancet* 1992; 339: 200-205.

9 Galen Choy C. Multiple Myeloma: Treatment recommendations. *Clin Immunother* 1995; 4: 346-360.

10 Alexanian R, Dimopoulos M. The treatment of multiple myeloma. *N Engl J Med* 1994; 330: 484-489.

11 Barlogie B, Jagannath S, Vesole DH, et al. Superiority of Tandem Autologous Transplantation over standard therapy for previously untreated Multiple Myeloma. *Blood* 1997; 89: 789-793.

12 McElwain TJ, Powles RL. High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. *Lancet* 1983; 1: 822-823.

13 Cunningham D, Paz-Ares L, Milan S, et al. High-dose melphalan and autologous bone marrow transplantation as consolidation in previously untreated myeloma. *J Clin Oncol* 1994; 12: 759-763.

14 Attal M, Harousseau JL, Stoppa AM, et al. A propective randomised trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med* 1996; 335: 91-97.

15 Henon P, Donatini B, Eisenmann JC, et al. Comparative survival, quality of life and cost-effectiveness of intensive therapy with autologous blood cell transplantation or conventional chemotherapy. *Bone Marrow Transplant* 1995; 16: 19-25.

16 Bensinger WI, Buckner D, Gharton G. Allogeneic stem cell transplantation for multiple myeloma. *Haematol Oncol Clin N Am* 1997; 11: 147-157.

17 Tricot G, Vesole DH, Jagannath S, et al. Graft-versus-myeloma effect: proof of principle. *Blood* 1996; 87: 1196-1198.

18 Bjorkstrand BB, Ljungman P, Svensson H, et al. Allogeneic bone marrow versus autologous stem cell transplantation in multiple myeloma: a retrospective case match study from the European Group for Bone and Marrow Transplantation. *Blood* 1996; 88: 4711-4718.

19 Gahrton G, Tura S, Ljungman P. Prognostic factors in allogeneic bone marrow transplantation for multiple myeloma. *J Clin Oncol* 1995; 13: 1312-1322.

20 Russell NH, Miflin G, Stainer C, et al. Allogeneic bone marrow transplant for myeloma. *Blood* 1997; 89: 2610-1611.

21 Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and non-malignant haematologic diseases. *Blood* 1998; 91: 756-763.

22 Gahrton G, Tura S, Ljungman P, et al. Allogeneic bone marrow transplantation in multiple myeloma. European Group for Bone Marrow Transplantation. *N Engl J Med* 1991; 325: 1267-1273.

23 Harousseau JL, Attal M, Divine M, et al. Autologous Stem Cell Transplantation after first remission induction treatment in Multiple Myeloma: A report of the French Registry on autologous transplantation in multiple myeloma. *Blood* 1995; 85: 3077-3085.

24 Fermand JP, Ravaud P, Chevret S, et al. High dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomised clinical trial. *Blood* 1998; 92: 3131-3136.

25 Cunningham D, Paz-Ares L, Gore ME, et al. High-dose melphalan for multiple myeloma: long-term follow-up data. *J Clin Oncol* 1994; 12: 764-768.

26 Anderson KC, Anderson J, Soiffer R. Monoclonal antibody-purged bone marrow transplantation therapy for multiple myeloma. *Blood* 1993; 82: 2568-2576.

27 Bjorkstrand BB, Ljungman P, Bird JM, et al. Autologous stem cell transplantation in multiple myeloma: results of the European Group for Bone Marrow Transplantation. *Stem Cells* 1995; 13: 140-146.

28 Fermand JP, Ravaud P, Chevret S, et al. High dose therapy and autologous blood stem cell transplantation in multiple myeloma: preliminary results of a randomised trial involving 167 patients. *Stem Cells* 1995; 13: 156-159.

29 Powles R, Raje N, Milan S, et al. Outcome assessment of a population-based group of 195 unselected myeloma patients under 70 years of age offered intensive treatment. *Bone Marrow Transplant* 1997; 20: 435-443.

30 Jagannath S, Barlogie B, Vesole DH, et al. Safety and efficacy of double transplant (DT) for newly diagnosed myeloma (MM) (Meeting abstract). *Proc Annu Meet Am Soc Clin Oncol* 1996; 15: A1398

31 Vesole DH, Tricot G, Jagannath S, et al. Autotransplants in Multiple Myeloma: What have we learned? *Blood* 1996; 88: 838-847.

32 Tricot G, Jagannath S, Vesole DH, et al. Peripheral blood stem cell transplants for multiple myeloma: identification of favourable variables for rapid engraftment in 225 patients. *Blood* 1995; 85: 588-596.

33 Corradini P, Voena C, Astolfi M, et al. High-dose sequential chemoradiotherapy in multiple myeloma: Residual tumour cells are detectable in bone marrow and peripheral blood harvests and after autografting. *Blood* 1995; 85: 1596-1602.

34 Lemoli RM, Fortuna A, Motta MR, et al. Concomitant mobilisation of plasma cells and haemopoetic progenitors into peripheral blood on multiple myeloma patients: positive selection and transplantation of enriched CD34+ cells to remove contaminating circulating tumor cells. *Blood* 1996; 87: 1625-1634.

Other papers published by the Trent Institute for Health Services Research are listed below:-

**Guidance Notes for Purchasers**

| | | |
|---|---|---|
| 96/01 | Working Group on Acute Purchasing: The Use of DNase in Cystic Fibrosis (1996) by JN Payne, S Dixon, NJ Cooper and CJ McCabe. | £6.00 |
| 96/02 | Working Group on Acute Purchasing: Tertiary Cardiology (1996) by J Tomlinson, J Sutton and CJ McCabe. | £6.00 |
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