WORKING GROUP ON ACUTE PURCHASING

The Effectiveness of High Dose Chemotherapy and Autologous Stem Cell Transplantation in the Treatment of Non-Hodgkin's Lymphoma and Hodgkin's Disease

July 1998

GUIDANCE NOTE FOR PURCHASERS 98/04

Series Editor: Nick Payne

InterDEC No: 11/1998

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 appropriate evidence, 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 21 July 1998 at which this Guidance Note for Purchasers (in a draft form) was considered.

THE EFFECTIVENESS OF HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA AND HODGKIN'S DISEASE

AUTHORS:

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EXPERT ADVISORS TO TRENT DEC:

Dr P Lorigan, Senior Lecturer in Medical Oncology, Weston Park Hospital, Sheffield
Mr SM Beard, Senior Operational Research Analyst, ScHARR and Ms F Sampson, Operational Research Analyst, ScHARR.

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

DECISION:

The Committee supported the use of high dose chemotherapy in those areas where there is clear evidence of efficacy from clinical trials, and supported its use for patients with conditions where clinical experience had shown clear evidence of benefits. These recommendations closely matched those produced by the European Blood and Marrow Transplant Registry.

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S M Beard
P Lorigan
F Sampson
A Sims

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Trent Institute for Health Services Research
Universities of Leicester, Nottingham and Sheffield

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Alison Ring
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SHEFFIELD S1 4DA

Tel 0114 222 0703
Fax 0114 272 4095
E-mail scharrlib@sheffield.ac.uk

Please make cheques payable to "The University of Sheffield"

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

AUTHORS

Mr S M Beard is a Senior Operational Research Analyst, School of Health and Related Research (ScHARR), University of Sheffield;
Dr P Lorigan is a Senior Lecturer in Clinical Oncology, Weston Park Hospital, Sheffield;
Ms F Sampson is an Operational Research Analyst, School of Health and Related Research (ScHARR), University of Sheffield;
Ms A Sims is an Epidemiologist in Public Health Medicine at Doncaster Health Authority.

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 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 Purchasing Authorities Chief Executives (PACE) 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/GLOSSARY

ABMT	Autologous Bone Marrow Transplantation
ABVD	Adriamycin, Vinblastine, Bleomycin, Dtic
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
BEAC	Busulphan, Etoposide, Cytarabine, Platinum
BEAM	Busulphan, Etoposide, Cytarabine, Melphalan
BMT	Bone Marrow Transplantation
BNLI	British National Lymphoma Investigations
BSBMT	British Society for Blood and Marrow Transplantation
ChIVPP	Chlorambucil, Vinblastine, Procarbazine, Prednisolone
CHOP	Cyclosphosphamide, Doxorubicin, Vincristine, Prednisolone
CML	Chronic Myeloid Leukaemia
CVB	Bcnu, Etoposide, Cyclophosphamide
DHAP	Cisplatin, Cytarabine, Dexamthasone
EBMT	European Blood and Marrow Transplant Registry
EORTC	European Organisation for the Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
F-MACHOP	Fluorouracil, Methotrexate, Cytarabine, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone
GELA	Group D'Étude des Lymphomas de l'Adulte
HD	Hodgkin's Disease
HDC	High Dose Chemotherapy
HLA	Human Leukocyte Antigen
HTA	Health Technology Assessment
LBL	Lymphoblastic Lymphoma

LDH	Lactoase Dehydrogenase
LYG	Life Year Gained
MACOP-B	Methotrexate with Leucovorin, Doxorubicin, Cyclophosphamide, Vincristine, Prednisolone and Bleomycin
MOPP	Mustine, Oncovin, Procarbazine, Prednisolone
MVPP	Mustine, Vinblastine, Procarbazine, Prednisolone
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
PABIOE	Procarbazine, Adriamycin, Bleomycin, Vincristine, Etoposide
PBPC	Peripheral Blood Progenitor Cells
PBSCT	Peripheral Blood Stem-Cell Transplantation
REAL	Revised European-American classification of Lymphoma
XRT	Radiotherapy

Autologous	A graft derived from the recepient of the graft
Allogeneic	A graft derived from another person other than an identical twin

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EXECUTIVE SUMMARY

Lymphoma and High Dose Chemotherapy

- Lymphomas are malignancies of the lymphoreticular system, which provides part of the body's natural defence against infection. Malignant lymphomas are categorised into two distinct disease types based on their underlying pathology, Non-Hodgkin's Lymphoma (NHL) and Hodgkin's Disease (HD).

- Current standard treatments for lymphoma are based on a combination of radiotherapy and chemotherapy, and depend on the type and stage of the disease. However, for more advanced stages of disease, the use of high dose chemotherapy (HDC) is becoming an increasingly common treatment option. Due to the high doses of drugs used, HDC causes irreversible bone marrow toxicity and requires patients to have follow-up blood support with either bone marrow transplantation (BMT) or, as has been the case more recently, with peripheral blood stem cell transplantation. In the case of lymphoma, these transplants are in the majority of cases autologous, using stem cells taken from the patients themselves via harvesting techniques.

- The European Blood and Marrow Transplant Registry (EBMT) is a collaborative group established in the 1980s which has drawn up draft accreditation guidelines for High Dose Chemotherapy Centres and these are likely to become accepted as minimum standards.

- The estimated cost of providing stem cell harvesting and HDC is £15,600. The estimated cost of standard salvage chemotherapy is £1,500 including an approximate 50% chance of further admission with neutropenic sepsis.

Non-Hodgkin's Lymphoma

- There are approximately 4,200 cases of NHL reported annually in England and Wales, approximately 8.0 per 100,000 per annum, with an underlying 3% increase in incidence. In 1994 there were 610 (288 female, 322 male) new registrations within the Trent Region.

- NHLs are a heterogeneous group of malignancies which tend to present and respond to treatment in very different ways. From a practical point of view, many clinicians divide NHL into low grade/indolent lymphomas and intermediate/high grade lymphomas.

- Low grade lymphoma accounts for around 30% - 35% of NHL, and is an indolent, insidious disease state which often has few symptoms and is often slow growing. Low grade NHL is characterised by a relapsing and remitting course with a median survival of between seven and nine years. High grade NHL accounts for around 65% - 70% of NHL and is an aggressive malignancy, treated mainly with combination chemotherapy. Approximately 80% of patients will achieve a complete remission with combination chemotherapy, but many relapse and only 40% of patients will be long-term survivors. There were 331 deaths from NHL within the Trent Region in 1994. Five year survival rates for NHL are 44% male and 42% female within Trent.

- The EBMT recommends the use of HDC in poor prognosis high grade NHL and first relapse high grade NHL. The EBMT suggests continued clinical trial in low grade NHL. The overall survival benefit of HDC in first relapse NHL is 13 months based on the Parma randomised controlled trial. This increases to 23 months when projecting benefits five years beyond the trial.

The cost per life year gained (LYG) for HDC in NHL based on trial data only is £12,818. The cost per LYG for HDC in NHL including five year projected benefits is £6,130.

Hodgkin's Disease

- There are approximately 1,100 new cases of HD reported each year in England and Wales, approximately 2.0 per 100,000 per annum. In 1994 there were 89 registrations of Hodgkin's disease within the Trent Region. There were 28 deaths from HD within the Trent Region in 1994. Five year survival rates for HD are 75% male and 61% female within Trent.

- Using established chemotherapy and radiotherapy regimens, over 80% of all patients can be cured of HD. Failure to achieve a complete response to treatment or relapse soon after chemotherapy is a poor prognostic factor.

- The EBMT recommends the use of HDC in first and subsequent relapsed HD, mantle cell lymphoma and lymphoblastic lymphoma.

- The overall survival benefit of HDC in relapsed and poor prognosis HD is 10 months based on the BNLI-Linch RCT. This increases to 19 months when projecting benefits five years beyond the trial.

The cost per LYG for HDC in HD based on trial data only is £17,625. The cost per LYG for HDC in HD including five year projected benefits is £6,130.

1. INTRODUCTION

1.1 Lymphoma: Background to Disease

Lymphomas are malignancies of the lymphoreticular system, which provides part of the body's natural defence against infection. Lymphoid tissue is found in most organs of the body and major groups of lymph nodes are found in the neck, ascillar, mediastinum, abdomen and groin. The tonsils, spleen and bone marrow are also considered as part of the lymphatic system.

Malignant lymphomas are categorised into two distinct disease types based on their underlying pathology, Non-Hodgkin's Lymphoma (NHL) and Hodgkin's Disease (HD). Non-Hodgkin's lymphoma is a much more heterogeneous group of conditions with a wide variety of histological types, clinical behaviour and treatment protocols. HD has well standardised histological classification, staging criteria and treatment protocols and accounts for approximately 20-30% of all lymphomas.

Current standard treatments for lymphoma are based on a combination of radiotherapy and chemotherapy, and depend on the type and stage of the disease. However, for more advanced stages of disease the use of high dose chemotherapy (HDC) is becoming an increasingly common treatment option, particularly with patients who have either relapsed after complete remission or have only achieved a partial response to standard treatment. Due to the high doses of drugs used, HDC causes irreversible bone marrow toxicity and requires patients to have follow-up blood support with either bone marrow transplantation (BMT) or, as has been the case more recently, with peripheral blood stem cell transplantation (PBSCT). In the case of lymphoma, these blood stem cell product transplants are in the majority of cases autologous, using blood stem cells taken from the patients themselves via harvesting techniques.

This increase in the use of HDC has not been based necessarily on a firm body of established randomised controlled trial (RCT) evidence. Much of the use of HDC has followed the positive results of smaller trials and studies.

The aim of this Guidance Note is to summarise the clinical evidence for HDC in the treatment of lymphomas, considering specific prognosis groups: complete remission; high risk; partial remission; first relapse; subsequent relapse. The Guidance Note also makes reference to an ongoing Health Technology Assessment (HTA) systematic review which is currently considering HDC treatment across a series of malignancies, including lymphoma.

Finally, the Guidance Note presents the potential cost-effectiveness of HDC when considered in patient groups where clinical effectiveness is confirmed by RCTs.

1.2 Non-Hodgkin's Lymphoma

1.2.1 Aetiology and Incidence

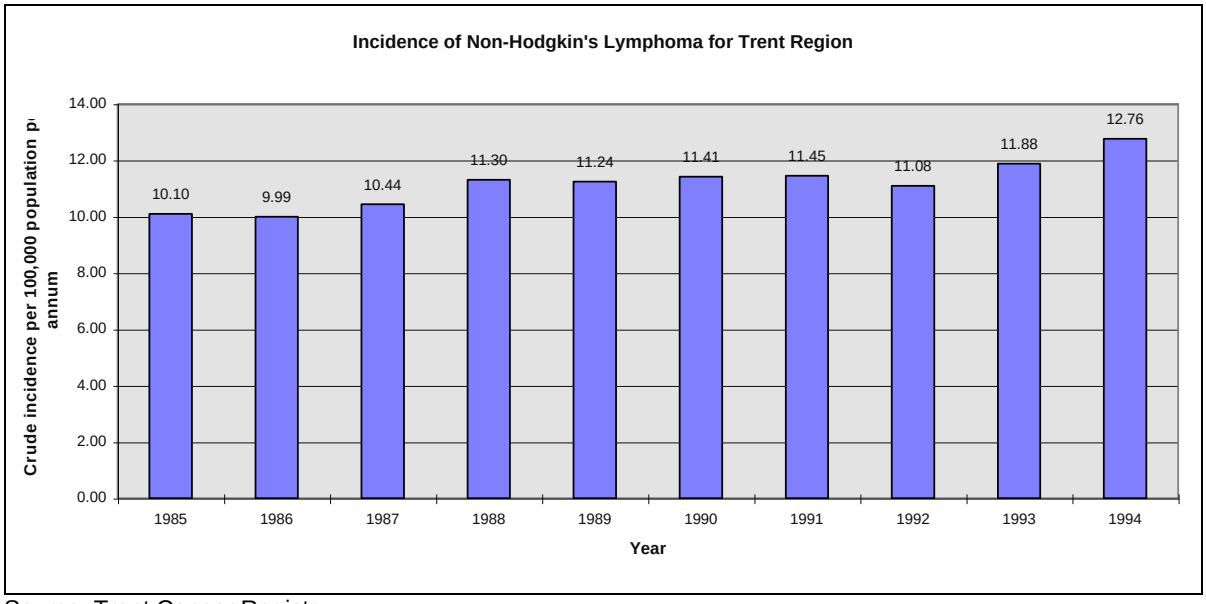
Non-Hodgkin's Lymphoma (NHL) is a heterogeneous group of conditions of which the incidence is rising by approximately 3% per year. There is an increased incidence associated with immunosuppression, autoimmune diseases, certain congenital disorders and AIDS. There appears to be a link to certain chemicals including hair dyes and pesticides. However, the cause for the rise in incidence is not immediately apparent and it does not appear to be solely accounted for by improvements in diagnostic techniques, registration of cases or increased prevalence of immunosuppressed patients. One third of cases are extra-nodal and may involve the skin, the gastrointestinal tract or any other organ.

There are approximately 4,200 cases of NHL reported annually in England and Wales, with 610 (288 female, 322 male) new registrations in the Trent Region in 1994. Crude incidence rates for Trent in 1994 are 11.9 per 100,000 per annum for females and 13.6 per 100,000 population per annum for males.

1.2.2 Histology

The histological classification of NHL is controversial. The Revised European-American classification of Lymphoma (REAL), based on cell lineage, morphology and distinct clinical entities, has now superseded the Working Formulation, which was based on cell lineage, cell type and grade. From a practical point of view, many clinicians divide NHL into low grade/indolent lymphomas and intermediate/high grade lymphoma.

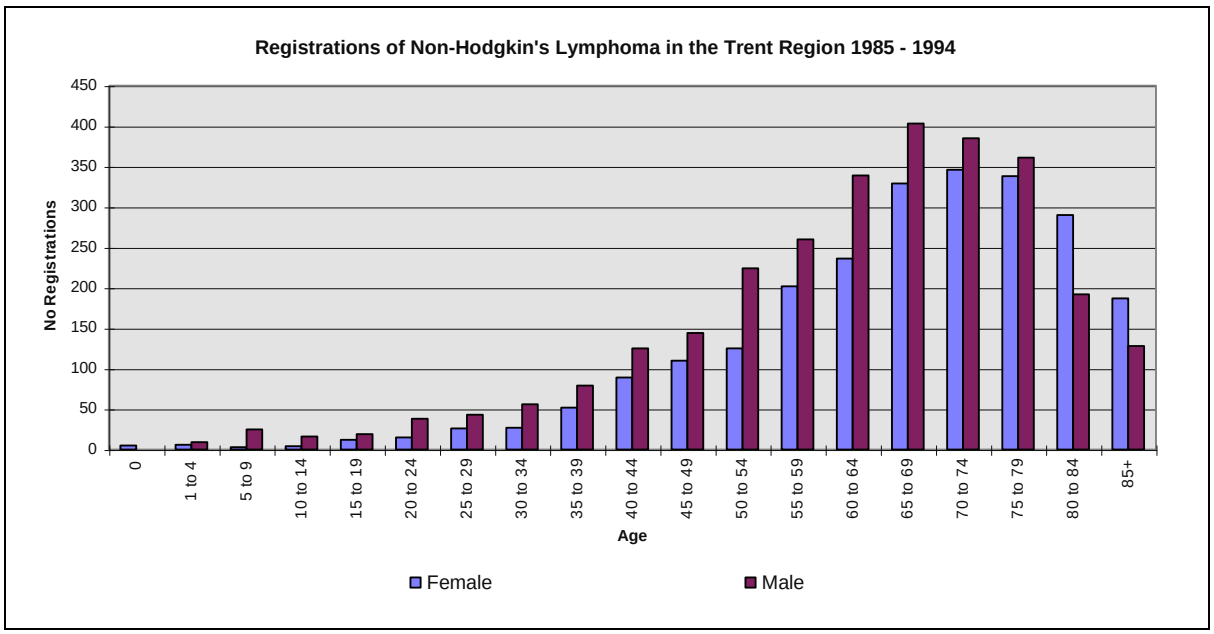
Figure 1 Trent Non-Hodgkin's Lymphoma Incidence Rate 1985-1994



Source: Trent Cancer Registry

Non-Hodgkin's lymphoma is more common in older age groups and shows a male preponderance.

Figure 2 Trent Age/Sex Non-Hodgkin's Lymphoma Notifications 1985-1994



Source: Trent Cancer Registry

1.2.3 Clinical Features

These are similar to those for HD, but patients often have widely disseminated disease. Bone marrow and extralymphatic organ involvement occurs more frequently than in HD and there may be an associated haemolytic anaemia or paraproteinaemia.

1.2.4 Staging

Staging is as for HD. The Ann Arbor classification is usually applied, although it is not always appropriate.

1.2.5 Treatment and Prognosis

Non-Hodgkin's Lymphomas are a heterogeneous group of malignancies which tend to present and respond to treatment in very different ways. They can be divided broadly into:

i) *Low Grade NHL*

Accounting for around 30% - 35% of NHL, low grade NHL is an indolent, insidious disease state which often has few symptoms at presentation and is often slow growing. Pathogenesis is characterised by a relapsing and remitting course with a median survival of between seven and nine years. Most patients present with disseminated disease. Treatment does not improve survival but is used for symptom control, and is usually with alkylating agents such as chlorambucil or with combination chemotherapy. Radiotherapy is very effective for control of local symptoms. A significant proportion of these low grade lymphomas subsequently transform into high grade lymphomas with a very poor prognosis.

ii) *High Grade NHL*

High grade NHL accounts for around 65% - 70% of NHL and is an aggressive malignancy, treated mainly with combination chemotherapy. Approximately 80% of patients will achieve a complete remission with combination chemotherapy but many relapse and only 40% of patients will be long-term survivors. Various initial chemotherapy regimens exist, but the gold standard remains CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone). A number of prognostic factors have been identified. These include age, stage, performance status, serum lactoase dehydrogenase (LDH) and involvement of extranodal sites. A prognostic score, the International Index, has been constructed and can predict those patients with a low probability of cure with conventional chemotherapy.

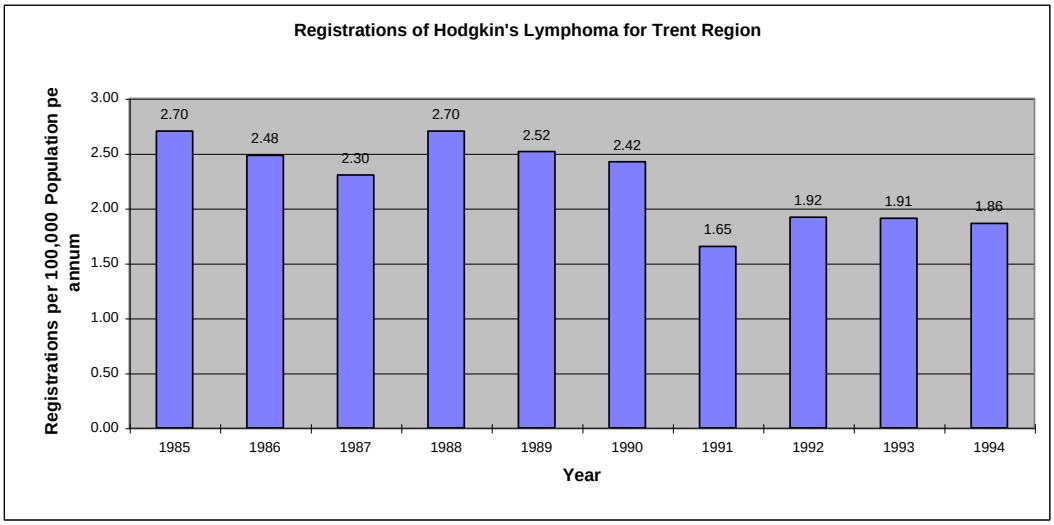
1.3 Hodgkin's Disease

1.3.1 Aetiology and Incidence

The incidence of HD is approximately 2.0 per 100,000 per year and is gradually falling. There are approximately 1,100 new cases reported each year in England and Wales. In 1994 there were 89 registrations of HD (44 female, 45 male) within the Trent Region, slightly lower than the expected national average. This translates into a crude incidence rate of 1.82 per 100,000 population per annum for females and 1.91 per 100,000 population per annum

for males in 1994.[1,2]

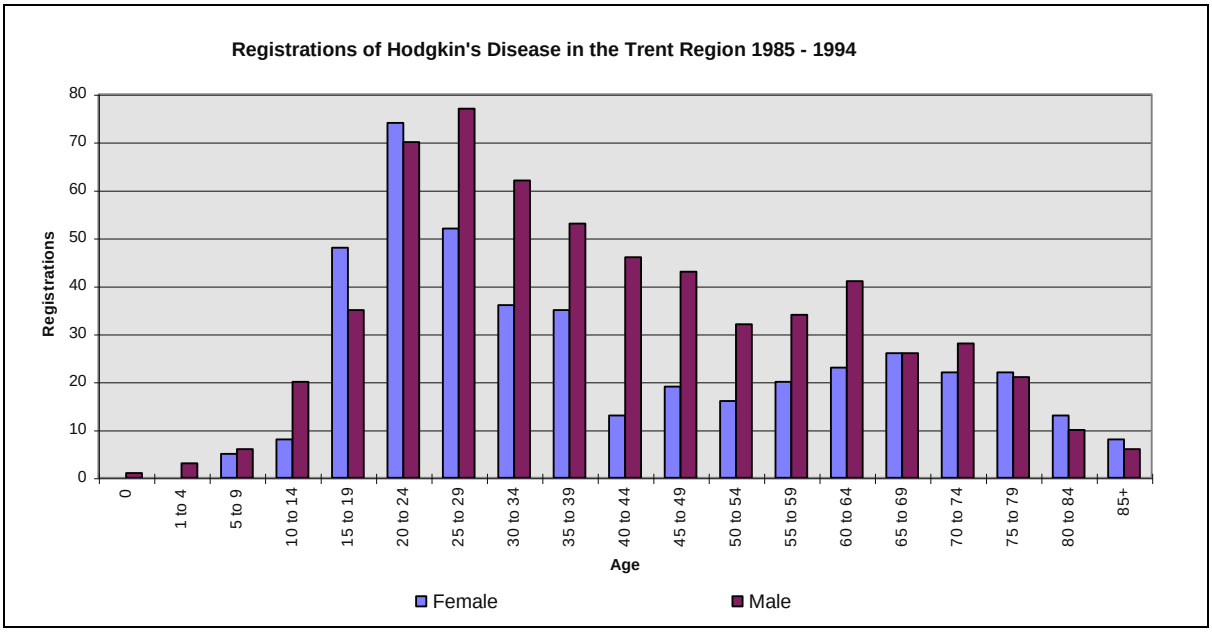
Figure 3 Trent Hodgkin's Disease Registration Rates 1994



Source: Trent Cancer Registry

There is a bimodal peak age incidence with one peak occurring at 15-34 years of age and the other after 50 years. There is a slight male preponderance in notification rates, see Figure 2.

Figure 4 Trent Age/Sex Hodgkin's Disease Notifications 1985-1994



Source: Trent Cancer Registry

The aetiology of HD is unknown, but there is mounting evidence to implicate Epstein-Barr Virus in at least one of the sub-types, with presence in 40% to 50% of HD cases.

1.3.2 Clinical features

Two thirds of cases present with cervical lymphadenopathy, although any lymph node group or extra nodal site may be involved. Patients may also complain of B symptoms i.e. high swinging temperatures, drenching sweats and weight loss of >10% of their body weight. Other symptoms may include pruritus, alcohol induced pain and a variety of other constitutional symptoms.

1.3.3 Diagnosis

A number of non-specific findings are commonly found including anaemia or raised Erythrocyte Sedimentation Rate (ESR). Diagnosis is established by demonstrating histological evidence of HD in a biopsy, usually of a lymph node. The cell type felt to be characteristic is the bi-nucleate Reed-Sternberg cell. This type of cell is specific to HD.

1.3.4 Histological classification

There are four main histological sub-types of HD in the Rye classification

a) Nodular sclerosing - accounts for 70% of cases

b) Lymphocyte predominant - accounts for 15% of cases

c) Mixed cellularity - accounts for 10% of cases

d) Lymphocyte depleted - accounts for 5% of cases

1.3.5 Staging

The stage of HD is currently classified using the Ann Arbor staging classification, developed in 1971, and later revised in 1989.

- Stage 1 - involves one lymph node group;
- Stage 2 - involves two or more lymph node groups;
- Stage 3 - involves lymph node groups on both sides of the diaphragm;
- Stage 4 - involves the extra nodal tissue, including bone marrow, liver, bone, lung, etc.

The staging of disease also takes into account the presence of a range of general symptoms:

- unexplained loss of body weight (>10% of pre-diagnosis weight);
- drenching night sweats;
- unexplained fever (>38 degrees C).

Patients are further sub-categorised within stage as:

- A - no general symptoms;
- B - presence of general symptoms.

A higher stage has a worse prognosis, and the presence of B symptoms indicates a worse prognosis independent of stage. A number of other prognostic factors have also been identified including lymphocyte count, lactoase dehydrogenase (LDH) and ESR. Prognostic scores have been constructed to identify patients with a poor prognosis. Clinical staging is carried out with a CT scan of the thorax and abdomen, chest X-ray and, where indicated, bone marrow trephine and aspiration.

1.3.6 Treatment

There are two effective treatments for HD, radiotherapy and combination chemotherapy. Radiotherapy is curative in HD if all the disease is treated with an adequate dose. Stages IA, IB and IIA disease are usually treated with radiotherapy although there is increasing evidence that a combination of low dose chemotherapy and involved field radiotherapy may be equally effective with reduced toxicity. Chemotherapy using four or more drugs, including an anthracycline, is used for stage IIB to stage IV disease. The gold standard regimen in the UK is currently an alternating regimen comprising eight drugs. This is currently being compared to the US gold standard of four drugs in a large national randomised controlled trial.

Using established chemotherapy and radiotherapy regimens, over 80% of all patients can be cured of HD. The chance of cure lessens with increasing stage, being >95% for stage I and approximately 60% for stage IV. Failure to achieve a complete response to treatment, or relapse soon after chemotherapy are both poor prognostic factors.

1.4 Prognosis and Mortality

The prognosis of both HD and NHL varies considerably according to the type and stage of the disease.

Prognosis is excellent for early stages of HD and is improving for all stages due to improvements in treatment. For more advanced stages, around 50% have long-term (over 10 year) survival.

Table 1 Overall Relative Survival Estimates - Hodgkin's Disease

Hodgkin's Disease	1 year	3 year	5 year
Male	85%	79%	75%
Female	80%	66%	61%

Source : Trent Cancer Registry

Prognosis for NHL is poorer, especially for stages III and IV, and is adversely affected by factors such as age. Some types of low grade NHL are also associated with a poor prognosis.

Table 2 Overall Relative Survival Estimates - Non-Hodgkin's Lymphoma

Non-Hodgkin's Lymphoma	1 year	3 year	5 year
Male	59%	46%	44%
Female	55%	45%	42%

There were 28 deaths from HD and 331 deaths from NHL within the Trent Region in 1994.

1.5 Scale of Problem in a 'Typical' District

In a 'typical' district of 500,000 people there would be approximately:

- 15 newly reported cases of low grade NHL per annum;
- 35 newly reported cases of high grade NHL per annum;
- 10 newly reported cases cases of HD per annum.

Within Trent HDC with stem cell transplantations are already being routinely used for patients with both relapsed HD and relapsed high/intermediate grade NHL.

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 is comprised of 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 EBMT for 1996 are now available and clearly show the commonest indications for HDC.

Table 3 High Dose Chemotherapy Notifications from EBMT Data

Disease Area	Notifications
Non-Hodgkin's Lymphoma	2,645
Breast cancer	2,156
Acute myeloid leukemia (AML)	1,878
Multiple myeloma	1,856
Chronic myeloid leukemia (CML)	1,382
Acute lymphoblastic leukemia (ALL)	1,275
Hodgkin's Disease	739

2. THE USE OF HIGH DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANTATION IN NON-HODGKIN'S LYMPHOMA AND HODGKIN'S DISEASE: SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Introduction to Treatment for Non-Hodgkin's Lymphoma

High dose chemotherapy, with the use of stored autologous bone marrow to rescue the patient from otherwise potentially lethal haematological toxicity, began to be used in significant numbers of patients with NHL in the late 1970s.[3]

The evaluation of HDC progressed through a number of stages. Initial studies were small phase II single institution studies. The procedure was initially performed in patients with extremely poor prognosis for whom it offered the only prospect of a cure. In the early 1980s the results of larger studies from collaborating, pioneering centres in co-operative groups began to suggest that remissions, if not cures, were possible.[4]

Peripheral blood is an alternative source to bone marrow of haematopoietic progenitors for transplantation after ablative therapy. Peripheral blood progenitor cells (PBPC) have the following advantages over bone marrow:

- Earlier engraftment leading to reduced procedure-related morbidity and mortality;
- No requirement for a general anaesthetic for the procedure to harvest the cells;
- Reduced risk of malignant contamination.

Over the last few years, there has been a rapid shift to the use of PBPC compared with bone marrow to support ablative chemotherapy.[5,6,7,8,9,10]

2.2 Intermediate and High Grade Non-Hodgkin's Lymphoma

2.2.1 HDC as Therapy in First Relapse Non-Hodgkin's Lymphoma

Approximately 70-80% of patients with high grade NHL achieve a complete response with first line chemotherapy, but a significant proportion relapse.

Parma Trial (Phillip)

In an initial pilot study, the Parma Group found that salvage chemotherapy followed by radiotherapy to the involved field, HDC and autologous bone marrow transplantation (ABMT) resulted in prolonged remissions in 40% of patients who had treatment sensitive lymphoma in relapse.[11] A further Parma randomised phase III controlled trial of 215 patients with relapsed NHL showed an initial response rate of 84% after HDC and 44% after standard salvage treatment. At five years the event-free survival was 46% in the high dose arm and 12% in the standard arm (p=0.001) and the overall survival rate was 53% in the high dose arm and 32% in the standard arm.[12,13]

A subsequent analysis of time to relapse in patients who received salvage chemotherapy showed that patients who relapsed within 12 months of the initial diagnosis had a high probability of relapse with resistant disease and suggested that this group of early relapse patients should be selected for further phase II studies, perhaps including double high dose procedure. However, even in this group, HDC was superior to conventional treatment.[14]

Summary: Based on these data, HDC with haematological rescue became standard treatment for patients with relapsed high grade NHL in sensitive relapse.[12,13] The Parma study is the only phase III trial in first relapse NHL.

2.2.2 HDC as Therapy in First Remission Intermediate and High Grade NHL

Patients with a high risk of relapse or failure to achieve complete remission after initial chemotherapy can be identified using the International Prognostic Index[15]. The long-term survival in this group of patients is in the order of 30%.

GELA Trial LNH-87 (Haioun)

The GELA group (Group D'Étude des Lymphomas de l'Adulte) carried out a randomised study comparing HDC with intermediate dose *consolidation* in patients in first complete remission with intermediate and high grade NHL. After induction 464 patients were assessable. With a median follow-up duration of 28 months, the three year disease-free survival rate was 52% in the standard arm and 59% in the high dose arm.[16] However, sub-group analysis showed that patients with at least two adverse prognostic factors who received HDC did better than those in the standard arm. Five year disease-free survival

was significantly higher in the ABMT arm (57 vs 36%, p=0.01) in the high-intermediate and high risk groups (2-3 factors, 236 patients); the 5-year survival rate also differed (65% vs 52%, p=0.06)[16,17] It was noticed in the study that only 65% of patients achieved a complete remission with their initial chemotherapy.

A non randomised comparison of conventional chemotherapy versus dose intensified plus *consolidation* HDC with peripheral blood progenitor cell rescue showed a significant reduction in event-free (61% vs 35%) and overall survival (64% vs 35%) at two years follow-up. There were 34 patients in the standard arm and 33 patients in the high dose arm.[18]

2.2.3 HDC as an initial therapy in High Grade Non-Hodgkin's Lymphoma

In view of the success of HDC in salvaging patients with relapsed high grade NHL and the ability to identify patients at high risk of relapse, investigators have also examined the effect of incorporating HDC early in the initial treatment regimen.

GELA Group Trial - LNH 93-3 (Gisselbrecht)[19]

The GELA group reported a randomised comparison of standard chemotherapy with CVB versus a short high intensive therapy with HDC on day 60, the LNH 93-3 protocol.[12] 302 patients with intermediate or high grade lymphoma with at least two adverse prognostic factors were included. The rate of induction failure was similar in both arms. With a median follow-up of 16 months, event-free survival was 57% in the standard arm and 48% in the high dose arm (p=0.02) and overall survival 73% in the standard arm and 61% in the high dose arm (p=0.01). A short induction treatment with HDC did not increase complete response rates when compared with standard treatment in this group.

INT Group Trial (Gianni)[20]

A further study carried out by the INT Group looked at intensive initial induction chemotherapy followed by early HDC treatment compared with standard alternating chemotherapy in adults with poor prognosis high grade NHL. 98 eligible patients were randomised to receive either standard or high dose sequential therapy. If the assigned treatment failed, the study design allowed patients to cross over to the other arm. After a follow-up of 55 months, the patients given high dose sequential therapy had a significantly higher rate of complete response when compared with the standard arm (96% versus 70%, p=0.001,) freedom from disease progression (84% versus 49%, p=0.001,) freedom from relapse (80% versus 70%, p=0.005,) and event-free survival (76% versus 49%, p=0.004.) Overall survival of seven years was better in the high dose arm, 81% versus 55%, but this

did not reach significance at conventional level (p=0.09.) Of note with this study, only 5% of those patients who failed standard chemotherapy could be salvaged by HDC, significantly lower than in other published studies.[20]

Summary: The place of HDC as initial treatment in high risk NHL remains unclear. A number of large studies are currently being undertaken by both the European Organisation for the Research and Treatment of Cancer (EORTC) and by the British National Lymphoma Investigations (BNLI). In addition, two randomised studies from a Dutch group and from the National Cancer Institute (NCI) completed recruitment in 1993 and results are awaited.

2.2.4 High Dose Chemotherapy in Patients with Incomplete First Response to First Line Chemotherapy.

The role of HDC in patients with NHL who have had a slow or incomplete response to initial chemotherapy has also been examined by a number of groups.

Martelli Trial[21]

An Italian co-operative group randomised 286 patients between two different alternating regimens F-MACHOP-B versus MACOP-B. Seventy seven (27%) patients had achieved only a partial response after completing two thirds of the first line chemotherapy and 49 (64%) of these were randomised to either standard salvage therapy with DHAP (27) or high dose chemotherapy with Busulphan, Etoposie, Cytarabie, Melphalan (BEAC) + Autologous Bone Marrow Transplantation (ABMT). The overall response rate was better in the high dose arm (96% vs 59%, p<0.001.) Projected progression-free survival at 55 months was 59% and 52% respectively and overall survival 73% and 73%. Neither was significant at conventional levels. The numbers studied were felt to be too small for a conclusion to be drawn.

Dutch/Belgian Trial[22]

A Dutch collaborative group randomised 69 patients with only a partial response after three cycles of CHOP to either ABMT or a further five cycles of CHOP. At four years, the overall survival was 85% in the CHOP group and 56% in the ABMT arm. The disease-free survival at four years was 72% and 60% respectively and the event-free survival 53% and 41% respectively. The authors concluded that there did not appear to be any advantage to the early use of HDC in patients with high grade NHL with a slow response to first line CHOP chemotherapy.

A non-randomised study from Canada[23] reported the results of 36 patients with NHL who had failed to achieve a complete remission with standard induction chemotherapy and who received HDC and ABMT rescue. The predicted three years overall survival (OS) was 51% and event-free survival (EFS) 39% with 28 months follow-up. In a similar group of patients with HD the EFS and OS at 35 months were 51% and 34% respectively.

Summary: To date, there is no proven survival advantage to early HDC in patients with a slow or incomplete response to CHOP chemotherapy.

2.3 Low Grade Non-Hodgkin's Lymphoma

2.3.1 Follicular lymphoma

Follicular lymphoma comprises 80% of low grade lymphoma. During the past 30 years, little significant progress has been made in the treatment of patients with advanced follicular NHL. Although the median survival time is 8-9 years, virtually all patients finally die of their disease after experiencing multiple remissions and relapses. Remissions can be induced either by single drug treatment, combination chemotherapy or chemotherapy followed by radiotherapy. However, none of these treatments has been shown to be associated with a survival advantage. A number of recent phase II clinical studies employing HDC and autologous stem cell rescue in patients with relapsed low grade malignant NHL have shown disease-free survival ranging between 60 and 85% at a median follow-up of 3-7 years. While these results are very encouraging, formal evaluation in randomised controlled trials is needed.[24]

2.3.2 Mantle Cell

Mantle cell lymphoma is an uncommon form of lymphoma previously classified as low grade,which is now being increasingly identified. It has a characteristic cytogenetic abnormality and is associated with poor prognosis; median survival is less than five years and less than 10% of patients are alive at 10 years. Patients usually present with widespread disease. Unlike most other types of lymphoma, mantle cell lymphoma is relatively chemotherapy resistant with a complete response rate of <30%. There may be a trend towards increased survival with anthracycline-based chemotherapy. In view of this resistance to conventional therapy, investigators have evaluated the role of HDC in first remission. There are no randomised controlled trials to date, but data from phase II studies

are mixed. The EBMT recommends HDC in first complete remission in mantle cell lymphoma.

The BNLI and EORTC are currently collaborating in a trial assessing the role of HDC as first line therapy in low grade NHL.

2.4 Lymphoblastic Lymphoma

Lymphoblastic Lymphoma (LBL) is a distinct sub-type of NHL. Characteristic features include male predominance, an increased incidence in adolescence and young adults and frequent mediastinal involvement at presentation. Bone marrow involvement is common and progression to leukaemic phase is a recognised terminal event. The clinical and pathological distinction between LBL and acute lymphoblastic leukaemia (ALL) is unclear. The two diseases have close morphologic and phenotypic similarities and overlap clinically. LBL in adults is a rare disease, accounting for approximately 4% of all adult patients with NHL. Therefore, it has been the subject of a relatively small number of studies. Early studies of childhood and adult LBL patients, treated with first and second generation chemotherapy regimens designed for intermediate grade NHL, reported poor results with long-term disease-free survival of only 15-30%. Substantial improvements in long-term survival were reported in the 1970s for children treated with regimens similar to those used for ALL and intensive chemotherapy and radiotherapy regimens for this type were subsequently adopted for adult patients, with an improvement in long-term, disease-free and overall survival to 40-60% in most series.

High dose chemotherapy has recently been used with encouraging results as consolidation of first remission in patients with LBL.

A review of 214 patients with LBL, reported to the EBMT between January 1981 and December 1992, included 105 patients undergoing HDC in first complete remission. The actuarial overall survival rate at six years for the entire group was 42%. Disease status at ABMT was the major determinant of outcome; six year actuarial overall survival was 63% for patients transplanted in the first complete remission compared with 15% of those with resistant disease at the time of transplantation. A second complete remission resulted in a 31% overall survival of six years.

The initial results of a randomised study carried out by the UK Lymphoma Group, comparing standard induction chemotherapy followed by either 'leukaemia style' maintenance therapy for 18 months or HDC have recently been reported. One hundred and eleven patients have entered the study. Patients with human leukocyte antigen (HLA) identical sibling donors were registered in the trial but treated with allogeneic BMT without randomisation in some centres. Data are currently available on the first 95 patients who entered the trial. Forty nine patients were randomised to maintenance chemotherapy or HDC. The actual overall survival at 18 months for all registered patients is 52%. Data for the individual treatment arms have yet to be published.

In the recently reported review from EBMT, allogeneic BMT was associated with a lower relapse rate than ABMT (24% versus 48%). The progression-free survival, however, was not significantly different because of the higher procedure related mortality.[25]

A number of small phase II studies have been carried out.[26,27,28]

2.5 Hodgkin's Disease

With the use of MOPP, MOPP alternatives such as MVPP and ABVD or hybrid regimens such as ChlVPP/PABlOE, the majority of patients with advanced HD can now be cured of their disease. However, a number of patients fail conventional treatment. Patients in whom chemotherapy fails can be divided into several important sub-groups based on the response to the initial chemotherapeutic regimens.

These include:

- patients with primary-refractory disease;
- patients who relapse within 12 months of completing chemotherapy;
- patients with multiple relapses.

Reported series have tended to include patients from all these patient groups.

2.5.1 HDC in Relapsed or Primary Refractory Hodgkin's Disease

A review of 107 patients with Hodgkin's Disease treated with combination chemotherapy at the National Cancer Institute showed that in those patients who did not achieve a complete

remission, relapsed within one year of completing treatment, or had more than one relapse, the chances of long-term survival were less than 20%.[29]

i) BNLI Trial (Linch)

A single RCT has been reported by the BNLI. Twenty patients with relapsed disease received sub-ablative chemotherapy with mini-BEAM and a further 20 received BEAM plus ABMT. The study closed early because of poor recruitment. There was a significant advantage for both event-free survival and progression-free survival in the HDC arm.[30]

The remaining evidence of effectiveness comes from a combination of smaller trials and observational studies.

Observational Studies

In one of the most quoted studies, University College Hospital, London reported a series of 155 poor risk HD patients who received HDC. All had either not attained a remission on MOPP type therapy and had poor prognostic features at presentation, not attained a complete remission or relapsed within one year after an initial alternating regimen or had failed two or more lines of treatment. The actuarial overall and progressive-free survival at five years were 55% and 50% respectively.[31]

Gianni et al.[32] reported on 25 patients with either refractory (seven patients), partial response (nine patients) or early relapse (nine patients) following induction chemotherapy with MOPP/ABVD. Event-free survival at six years was 78% for those with short initial complete responses and 31% for patients who had primary-refractory disease.

Fifty one patients with either primary-refractory or relapsed HD were treated by a German group[33] with salvage chemotherapy followed by HDC. Patients had received a median of three different courses of chemotherapy and 84% had received radiotherapy either as involved field, mantle, inverted Y or total nodal irradiation. Eight patients had primary refractory disease. With a median follow up of 12 months, overall survival was 61% and progression-free survival 44%.

Armitage et al. [34] reported the use of CVB and ABMT in 70 patients treated between 1984-88. Overall survival at four years was 47% and disease-free survival was significantly better for those patients treated in first relapse as compared to those treated in subsequent relapse.

A French study examined 100 patients with HD who had either failed to respond to front line chemotherapy (n=41) or relapsed, (n=59) and were treated with salvage chemotherapy

followed by HDC.[35] 59% of patients had achieved a complete response with a re-induction chemotherapy and 72 patients went on to receive HDC. The estimated two year survival for the 100 patients was 59%, or 61% of those who received HDC. However, 47 of the 72 patients who received HDC had either not responded to, or only achieved a partial remission with, re-induction chemotherapy.

A further study looking at the role of HDC with CBV and ABMT in relapsed HD after two lines of chemotherapy reported an event-free and overall survival rate at five years of 53% and 47% respectively.[36]

A retrospective analysis of 86 patients with refractory HD from 14 centres in France treated with ablative chemotherapy showed that with a median follow-up of 29 months, the overall survival was 35%. Comparative data from the EORTC, Group D'Étude des Lymphoma de l'Adulte (GELA) and IDHG databases showed that the reference population had a five year survival of 20%.[37]

A review of the EBMT data for 290 patients treated with primary-refractory HD between 1979-1995 showed an actuarial five year progression-free survival and overall survival to be 30% and 31% respectively.[38]

The use of CBV +/- cisplatin has been reported in primary refractory HD. The progression-free survival in 30 patients treated was 42% at 3.6 years with an overall survival of 60% at five years.[39]

Summary : Based on the above and other studies, standard treatment for patients with refractory HD (i.e. less than a complete response after first line therapy), relapse within 12 months of completing treatment or more than one relapse, is now HDC. There may also be a survival benefit for patients who relapse more than one year after completing first line chemotherapy. The EORTC are currently carrying out a randomised trial of conventional salvage versus HDC in relapsed HD.

2.5.2 HDC in First Remission Hodgkin's Disease

A number of independent prognostic factors have been identified for HD and a prognostic score constructed.[40] A number of studies looking at the role of HDC in first complete remission or good partial remission are ongoing. These include studies by the EBMT and by the Scottish and Newcastle Lymphoma Group.

2.5.3 Timing of HDC in Relapsed Hodgkin's Disease

The optimum timing for HDC in relapsed HD remains undecided. There has been a tendency to adopt a similar strategy to NHL, i.e. to demonstrate chemosensitivity and reduce tumour bulk with re-induction chemotherapy. However, there is some evidence that in fit patients it may be better to proceed directly to a high dose procedure. Bierman et al. reported the use of ABMT or PBPC in 84 patients with HD in first relapse.[41] All patients were transplanted with the CVB regimen. 73 of the 84 patients received a brief course of chemotherapy before coming to HDC. 63% of patients achieved a complete response following the HDC and there was a 4% treatment related mortality. The progression-free survival at four years for this group was 43%. A sub-set of patients who came immediately to transplant without any low-dose salvage therapy had a failure-free survival at four years of 91%.

A recently presented review of the EBMT database suggested that in patients with first relapse, those who had a relapse greater than one year still benefited from HDC when compared with standard salvage in historical controls. Furthermore, there was no benefit to demonstrating chemosensitivity and the recommendation was that patients should proceed to HDC immediately. Five year actuarial survival in the 139 patients was 49.4%, progression-free survival 44.7%.

There appears to be an increasing body of evidence that in patients with relapsed HD, it is advantageous to proceed directly to HDC without re-induction chemotherapy to demonstrate chemosensitivity. However, many patients with relapsed HD may not be fit for an immediate high dose procedure. Because of disease-related problems in these patients re-induction chemotherapy is still indicated.

2.6 Source of Progenitors in Non-Hodgkin's Lymphoma; Autologous Versus Allogeneic (Donor)

Although most patients with lymphoma have been transplanted with autologous bone marrow or peripheral blood stem cell, approximately 10% of transplants have been performed with allogeneic marrow. The use of allogeneic marrow (alloBMT) eliminates the possibility of infusing malignant cells into the transplant recipient. In addition, autologous bone marrow transplantation (ABMT) has potential for a graft versus lymphoma effect similar to the graft versus leukaemia effect seen in some types of leukaemia.

Disadvantages of ABMT include high transplant related morbidity and mortality due to graft versus host disease. In addition, only one third of patients will have a suitably matched donor and patients may be considered too old for ABMT.

Investigators at John Hopkins University, USA, reported outcomes in patients undergoing allogeneic transplantation for NHL and HD.[43] The relapse rate was 46% for recipients of autologous bone marrow compared with 18% for patients who received allogeneic marrow. However, the higher relapse rate in patients who received autologous marrow was offset by higher transplant related mortality in patients who received allogeneic transplants. The EFS in the two groups was not significantly different.

A case controlled study of patients reported to the EBMT matched 101 ABMT patients with 101 patients who underwent allogeneic transplantation. The progression-free survival was similar in both types of transplants (46% vs 49% respectively). The overall relapse and progression rate for the allogeneic BMT was 23% compared with 38% in the ABMT patients, but failed to statistical significance.[42]

2.7 Indications for High Dose Chemotherapy in Lymphoma

The EBMT has drawn up draft accreditation guidelines for HDC Centres and it is likely that these will be accepted as minimum standards. Indications for HDC have also been drawn up by the EBMT and it is likely that these will be adopted as the current indications for HDC. An edited version of these guidelines for lymphoma is shown below.

Table 4 EBMT Draft Guidelines for High Dose Chemotherapy Indications in Lymphoma

Disease	EBMT DRAFT RECOMMENDATIONS				Trent WGAP Clinical Interpretation
	Status	Allogeneic - Sibling	Allogeneic - Unrelated	Autologous	Autologous
Intermediate/High grade NHL	Initial treatment	-	-	-	CT
	First partial response	-	-	-	CT
	First complete remission (consolidation)	R	CT	R	CT
	First relapse	R	D	R	R
Low grade NHL	First complete remission	NR	NR	CT	CT
	First relapse	CT	NR	CT	CT
	Second complete remission	CT	NR	CT	CT
Lymphoblastic NHL	First complete remission	CT	D	R	Not Discussed
	Established relapse	D	NR	NR	Not Discussed
Mantle Cell Lymphoma	First complete response	R	-	R	Not Discussed
Hodgkin's Disease	First relapse	R/CT	D	R	R
	Refactory disease - no response	CT	D	D	CT
	Second or subsequent relapse	R/CT	D	R	R
	First complete remission (consolidation)	D	NR	CT	CT
	First partial response	R/CT		R	R

CT	Clinical trial	The value of transplants in this group has not yet been clearly defined. Patients should be treated as part of a clinical trial.
R	Recommended	The results of such procedures are well defined and compare favourably (often better) than standard treatment.
D	Developmental	There is little or no national experience of HDC in this setting.
NR	Not recommended	There is some overlap with the developmental recommendation. It essentially covers diseases not usually treated with HDC and includes early stage disease for which the additional risk of HDC is not justified

Note: There are still questions remaining over the exact interpretation of EBMT guidelines in HD.

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

3.1 General

From the review of the clinical evidence, it is apparent that HDC is indicated as a clinically effective and recommended therapy in four specific patient prognosis groups:

- Non-Hodgkin's Lymphoma - First relapse
- Hodgkin's Disease - First relapse
- Hodgkin's Disease - Second or subsequent relapse
- Hodgkin's Disease - Primary refractory disease (i.e. incomplete response)

HDC is also recommended in the EBMT draft guidelines for Lymphoblastic NHL and mantle cell lymphoma. As this represents a very small proportion of lymphoma, no separate cost benefit has been considered.

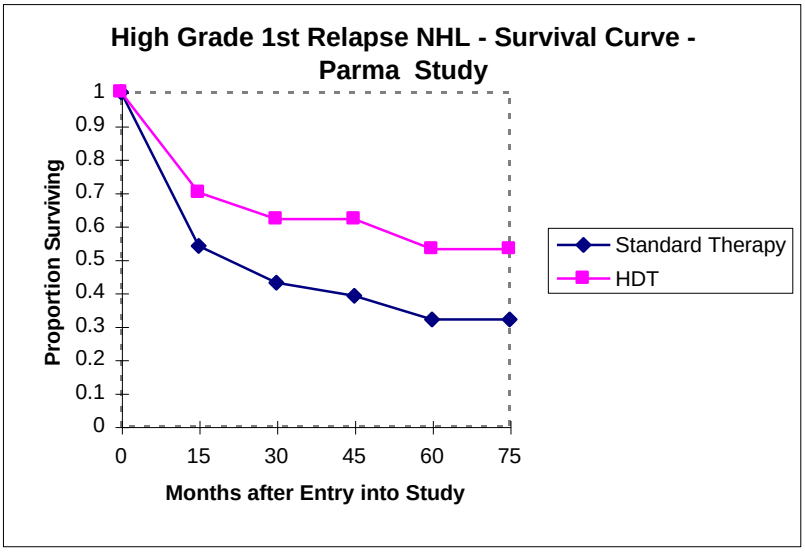
Non-Hodgkin's low grade and first complete response HD remain areas where clinical benefit has yet to be proven through randomised controlled trial evidence.

The following considers the level of patient benefit that can be derived in each patient group from the trial evidence.

3.2 Benefits of High Dose Chemotherapy in First Relapse Non-Hodgkin's Lymphoma

The main evidence for benefit in this group comes from the Parma study.[11] The study provides evidence of both overall survival and disease-free survival at the five year point. Unfortunately, the study does not provide any exact data points within the five year period, but does present a Kaplan-Meier curve of the survival data. Using the published data and graphs both benefits have been estimated in order to make a direct comparison between the standard chemotherapy arm and the HDC study arm.

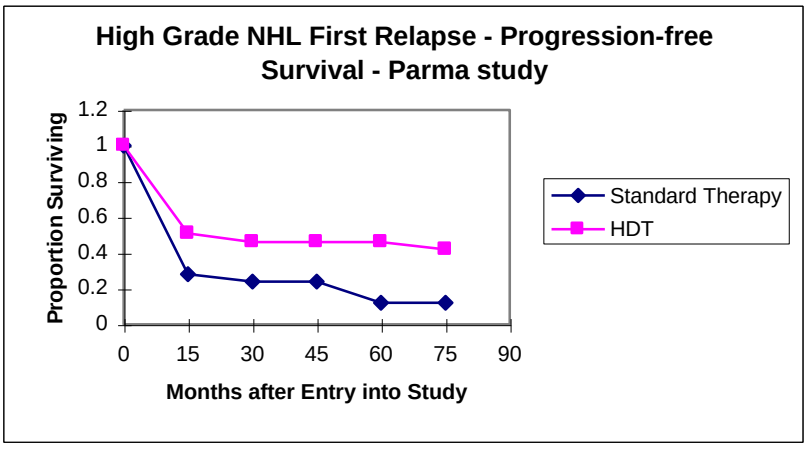
Figure 5 Non-Hodgkin's's Lymphoma Parma Study - Overall Survival Curves



Using these curve estimates it is predicted that the marginal survival benefit of HDC over standard chemotherapy is approximately 13 months (49 months c.f. 36 months) after a period of 75 months, which translates into a 1.1 life year gained (LYG). The estimate is taken as the difference between the area under the curve up to the end of trial results, in this case 75 months. In the absence of trial data, the area under the curve is taken using straight line interpolations between data points taken at 15 month intervals from the original Kaplan-Meier curves.

In a similar way the disease-free survival data can also be used to make comparisons.

Figure 6 Non-Hodgkin's's Lymphoma Parma Study - Disease-free Survival Curves

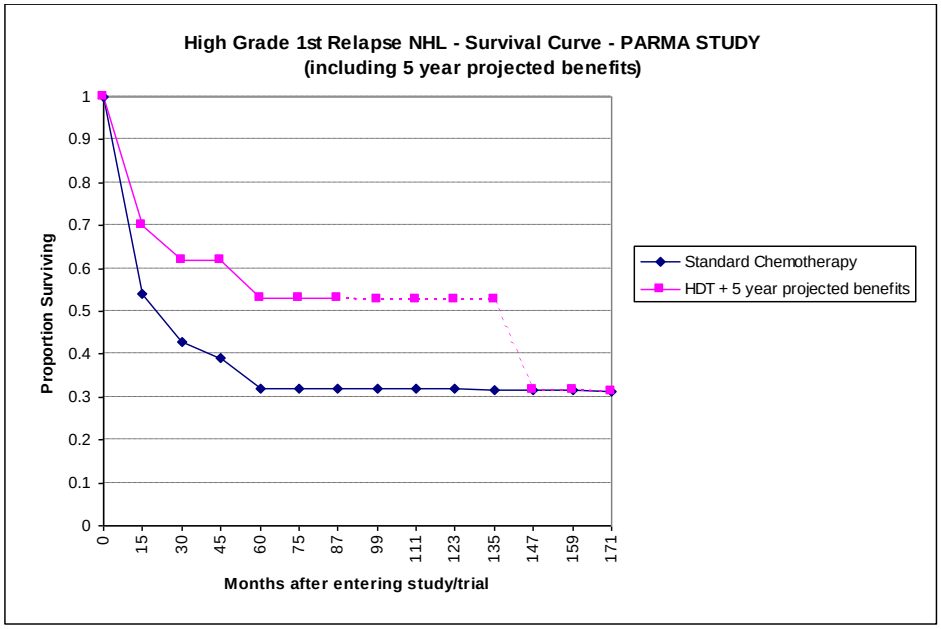


Using these curve estimates it is predicted that the marginal disease-free survival benefit of HDC over standard chemotherapy is approximately 17 months (39 months c.f. 22 months).

Calculating benefits in this way ignores any benefit which may follow on from the trial end-point. Whilst these benefits carry a degree of uncertainty, as they remain unrecorded in trial, it is still appropriate to estimate their likely magnitude under a range of different assumption scenarios.

The most pessimistic case would be that immediately after the 75 months trial period the HDC treatment arm moves immediately to the outcome curves of the conventional treatment group. This is obviously highly unlikely as it would require an immediate increase in death rate. As the survival curves flatten out for both treatment arms the five year trial survival has been taken to indicate a long-term cure. Taking the overall survival curve it has been assumed that the benefits of treatment continue at the same level, representing no further lymphoma related mortality, for a range of period from five years to 30 years at which point the two treatment groups are assumed to merge together.

Figure 7 Projected Survival Benefits of High Dose Chemotherapy



The graph above shows the projected outcome curve for the five year projection scenario.

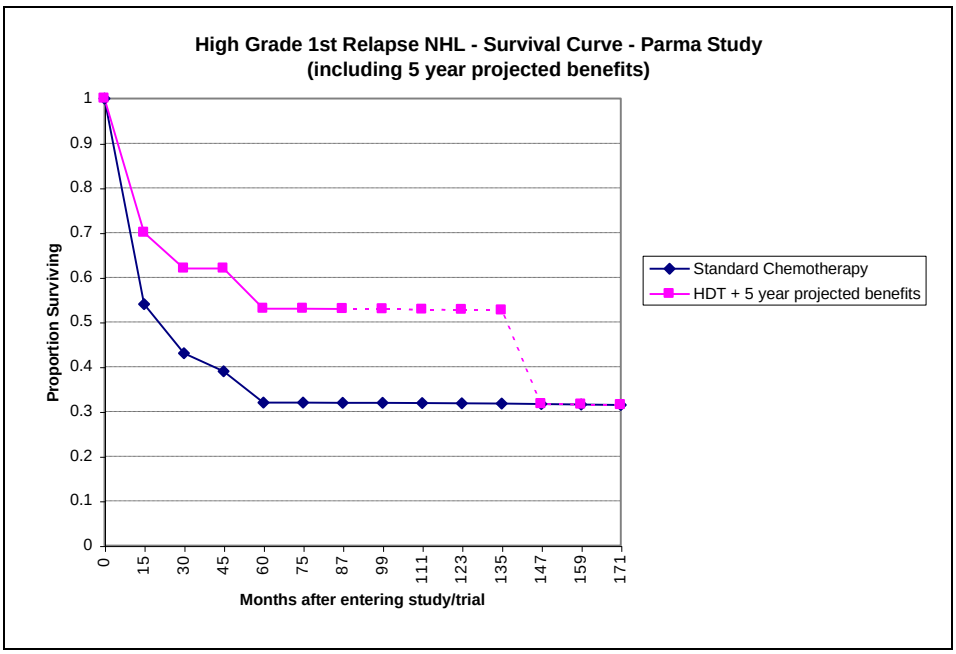
Adopting these assumption scenarios beyond the 75 month point, a set of revised estimates of marginal survival benefit are arrived at, as presented in the table below.

Table 5 Parma Trial Survival Benefits

Forward Projection of End of Trial Benefits	Survival Benefit in Months	LYG
5 year	27mths (85mths c.f. 58mths)	2.3
10 year	40 mths (116mths c.f. 76mths)	3.3
20 year	66 mths (182mths c.f. 116mths)	5.5
30 year	82 mths (224mths c.f. 142mths)	6.8

In a similar consideration of disease-free survival:

Figure 8 Projected Disease-free Benefits of High Dose Chemotherapy



Adopting the same scenarios about the benefits beyond the 75 month point, revised estimates of marginal survival benefit are arrived at.

Table 6 Parma Trial Event-free Survival Benefits

Forward Projection of End of Trial Benefits	Event-Free Benefit in Months	LYG
5 years	37 mths (67mths c.f. 30mths)	3.1
10 years	55 mths (92mths c.f. 37mths)	4.6
20 years	92 mths (144mths c.f. 52mths)	7.7
30 years	116 mths (178mths c.f. 62mths)	9.7

The table below summarises the estimated clinical benefits derived from the Parma study.

Table 7 Clinical Benefits of Parma Study

Benefit	Based on Trial Period Only	Including Short-term Benefit Estimates (5 years)	Including Long-term Benefit Estimates (30 years)
Overall Survival	13 mths	27 mths	82 mths
Event-Free Survival	17 mths	37 mths	116 mths

3.3 Benefits of High Dose Chemotherapy in Hodgkin's Disease

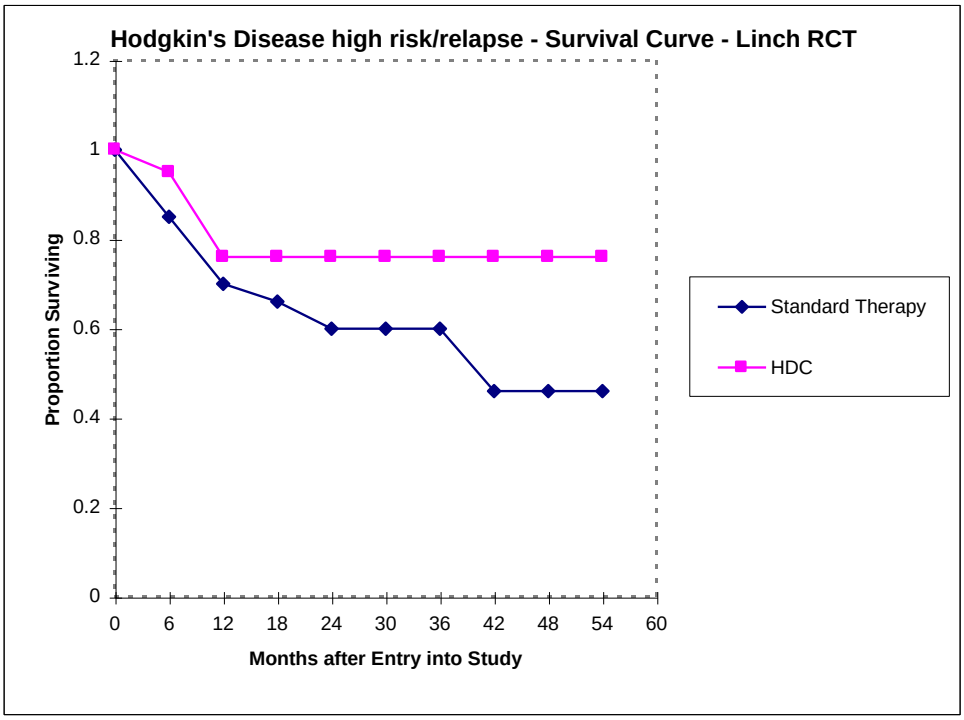
As stated, the studies and trials related to HD tend to consider groups of mixed patients combining treatment refactory with relapse patients. Two possible sources of clinical benefit are considered.

BNLI-Linch RCT Trial

The Linch trial[30] is the only published RCT considering HDC in HD. The trial considers a mixed patient group consisting of 40 treatment failed patients, 26 short of full recruitment due to patient refusal in favour of HDC. The two arms compared HDC based on BEAM+ABMT against mini-BEAM (lower dosage of the same drug combination).

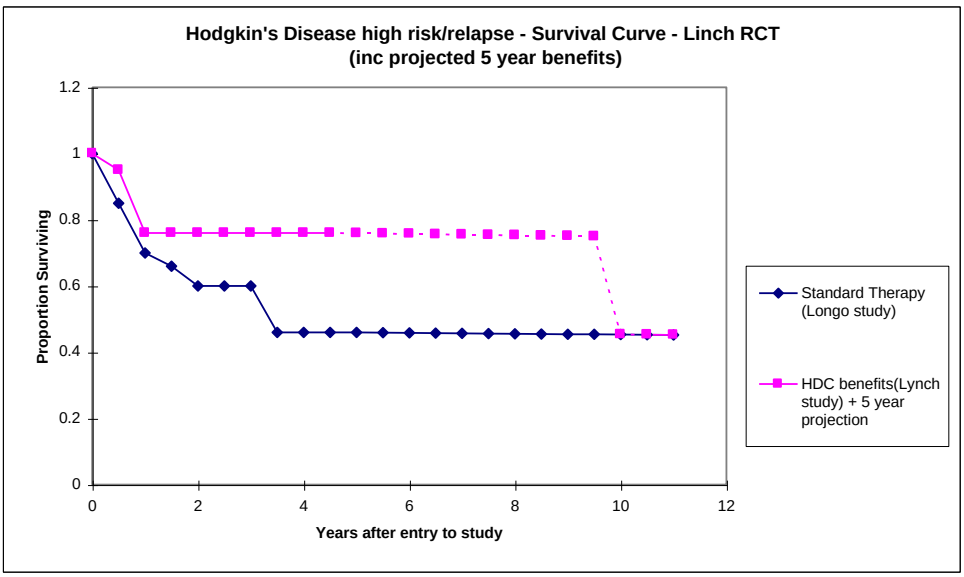
The survival benefit is shown in the following graphs with and without a five year extended benefit approximation.

Figure 9 **High Dose Chemotherapy Survival Benefit in Relapses/Treatment Failure Hodgkin's Disease - Linch Randomised Controlled Trial**



From these graphs using the same area under the curve approximation methodology as used in NHL, it is estimated that, using purely the trial data, the marginal survival benefit is 10 months (66 months c.f. 56 months).

Figure 10 **High Dose Chemotherapy Survival Benefit in Relapses/Treatment Failure Hodgkin's Disease - Linch Randomised Controlled Trial**



A range of projected benefit scenarios considering outcome 5, 10, 20 and 30 years beyond the trial end-point have also been considered. The analysis includes a standard mortality for each projected year and again compares the area under the curve up to the point where the two treatment arms merge. The results of this analysis are shown in the following table.

Table 8 BNLI-Linch Trial Survival Benefits

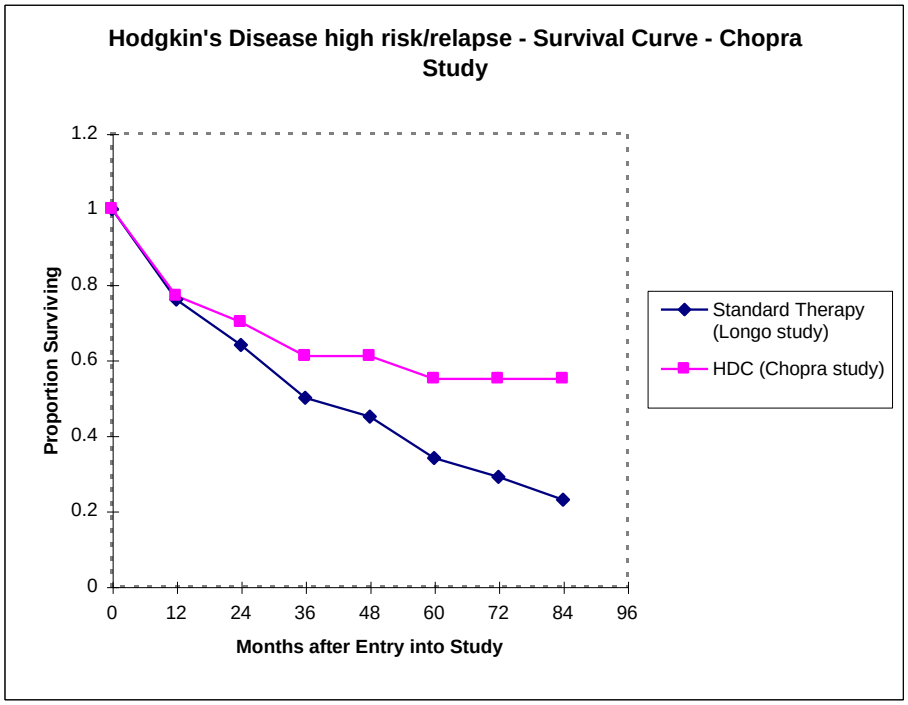
Forward Projection of End of Trial Benefits	Survival Benefit in Months	LYG
5 years	28 mths (92mths c.f. 64mths)	2.3
10 years	45 mths (136mths c.f. 91mths)	3.8
20 years	78 mths (220mths c.f. 142mths)	6.5
30 years	105 mths (290mths c.f. 184mths)	8.8

Chopra Study

Although the Linch RCT is the only randomised trial, there are a number of retrospective studies and patient follow-up studies which have monitored and observed the benefits of HDC in this patient group. The largest of these is the Chopra study[31] which followed up eight years' data related to 155 poor risk HD patients, who had received BEAM treatment with ABMT. All these patients had partial response or relapse on conventional chemotherapy.

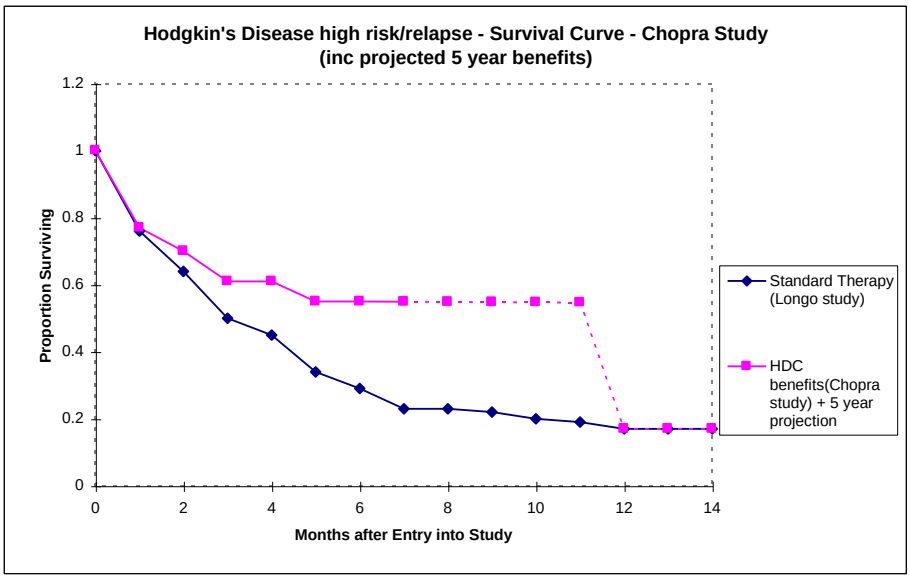
The following compares these observational data to the findings of another study, Longo et al.,[29] which reported the low probability of cure from standard chemotherapy treatment in a similar mix of treatment resistant and relapsed patients. This study noted a 17% survival rate at five years on standard therapy, matching other reported series.

Figure 11 **Benefits of High Dose Chemotherapy in Hodgkin's Disease - Chopra c.f. Longo Study**



From these graphs using the same area under the curve approximation methodology and trial data only, the marginal survival benefit is 11 months (65 months c.f. 56 months).

Figure 12 **Benefits of High Dose Chemotherapy in Hodgkin's Disease - Chopra c.f. Longo Study**



By including an extra five years' projected benefits at a constant rate before bringing the HDC group back to the standard treatment arm, this marginal survival benefit increases to 30 months (86 months c.f. 56 months).

Table 9 Chopra - Longo Study Comparison Survival Benefits

Forward Projection of End of Trial Benefits	Survival Benefit in Months	LYG
5 years	30 mths (85mths c.f. 55mths)	2.5
10 years	52 mths (118mths c.f. 66mths)	4.3
20 years	95 mths (181mths c.f. 86mths)	7.9
30 years	132 mths (234mths c.f. 102mths)	11.0

The following table summarises the clinical benefits of HDC in Hodgkin's Disease.

Table 10 Clinical Benefits of High Dose Chemotherapy in Relapsed and Poor Prognosis Hodgkin's Disease

Benefit	Based on trial period only	Including short-term benefit estimates (5 years)	Including long-term benefit estimates (30 years)
Overall Survival - Linch RCT (5 year study follow-up)	10 months	28 months	105 months
Overall Survival - Chopra Study c.f. Longo Study (6 year study follow-up)	11 months	30 months	130 months

It is interesting that both the Randomised Controlled Trial and the observational retrospective patient follow-up show similar survival benefits. For the purpose of the economic evaluation, the analysis is limited to the Linch randomised controlled trial evidence only.

3.4 Cost of High Dose Chemotherapy

The relative costs of treatment for lymphoma have been sourced from Weston Park Hospital, Sheffield and are based on a combination of drug, staffing and bed costs (where appropriate).

The significant areas of difference between standard chemotherapy and HDC regimens are the need for the harvesting procedure and the requirement for in-patient and day case facilities/care.

The cost of providing stem cell harvesting and HDC is estimated at £15,600, based on general extra contractual charges for procedures. This cost is appropriate for the majority of HDC in both Non-Hodgkin's Lymphoma and Hodgkin's Disease cases as most patients have the same type of therapy.

The cost of providing a standard chemotherapy regimen is estimated at between £1,200 - £1,500. The cost of standard salvage chemotherapy is calculated from the cost of the drugs for one particular regimen including a 50% chance of admission because of neutropenic fever. It does not include any in-patient costs which may be associated with the chemotherapy alone. Therefore, it can be considered to be an underestimate of the treatment cost.

Another important point is that standard dose salvage therapy is successful in the minority of patients only. The majority of patients, around 70%, will relapse again needing further treatment, blood transfusions, radiotherapy, analgesia etc. High dose patients who relapse tend to have very aggressive disease and do not survive for very long. Therefore, the cost of palliative care in the standard therapy patients is likely to be higher than calculated.

In an attempt to quantify the level of relapse costs, the patient records of four patients who had standard chemotherapy for HD with a later event of relapse were reviewed. The patient records identified areas of resource use including: palliative chemotherapy, radiotherapy, hospital admissions, blood tests, scans, blood transfusions, antibiotics etc. Based on these records, it is calculated that the mean average cost of relapse treatment is around £9,500, although costs ranged from £4,000 to £15,000. Importantly, this cost estimate does not include any hospice costs or costs outside the secondary care sector.

Although it is important to recognise these very real extra support costs of relapse under standard therapy, the economic analysis has been based firmly on first line treatment costs only. On a one-to-one comparison, the marginal cost of a single course of HDC is estimated at £14,100-£14,400. There are no other differences in costs envisaged in the provision of HDC as the infrastructure to support treatment remains the same.

3.5 Cost-Benefit of High Dose Chemotherapy in Non-Hodgkin's's Lymphoma

In considering the cost benefits of adopting HDC in first relapse NHL, the overall survival benefit is compared with the implied marginal costs. The marginal survival benefit as implied by the trial data only is considered first. This is in effect assuming that, at the 75 month point, the HDC cohort reduces immediately to the survival level of the standard chemotherapy treatment group. This is obviously pessimistic, but represents the data that are known and reported in the literature.

Table 11 Cost-effectiveness of High Dose Chemotherapy in Non-Hodgkin's Lymphoma: Trial Based Data

Cost-effectiveness Based on Trial Data Only (75 Months)	Standard Chemotherapy	High Dose Therapy	Marginal Survival Analysis
Therapy Cost	£1,500	£15,600	£14,100
Survival (area under the curve estimate)	36 months	49 months	13 months
	3.0 LYG	4.1 LYG	1.1 LYG
Marginal Cost per LYG	-	-	£12,818

Based on this analysis it is predicted that HDC provides a marginal 1.1 LYG per patient at an increase in treatment cost of £14,100. This translates into a cost per LYG of £12,818.

Consideration can also be given to this analysis taking into account the predicted extended benefits based on the five year projection of ongoing treatment benfits. At the five year point, the HDC group is reverted to standard chemotherapy survival levels. Under this scenario the marginal survival benefit increases to 2.3 LYG.

Table 12 Cost-effectiveness of High Dose Chemotherapy in Non-Hodgkin's Lymphoma: Extended Benefits Assumed

Benefit	Standard Chemotherapy	High Dose Therapy	Marginal Analysis
Therapy Cost	£1,500	£15,600	£14,100
Survival (area under the curve estimate)	58 months	85 months	27 months
	4.8 LYG	2.5 LYG	2.3 LYG
Marginal Cost per LYG	-	-	£6,130

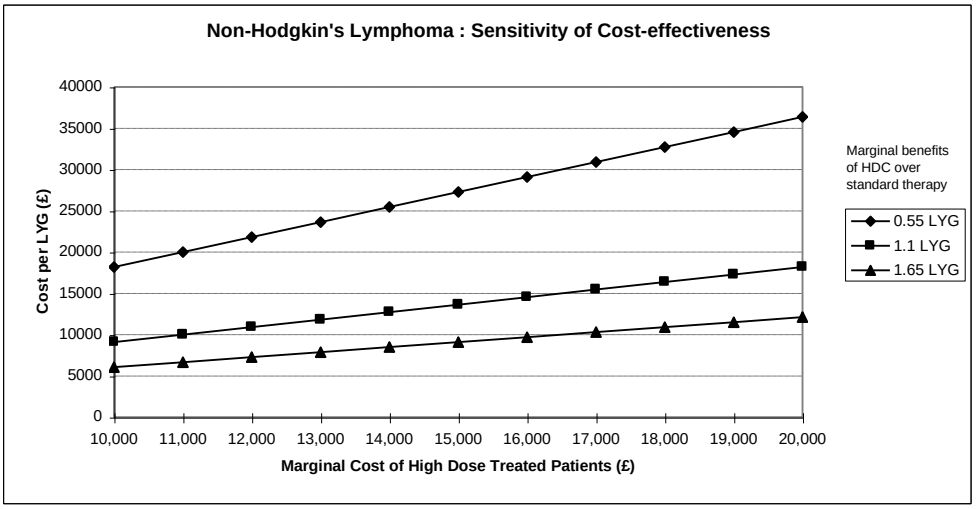
The cost per LYG including 5 year projected benefits = £6,130
The cost per LYG including 10 year projected benefits = £4,272
The cost per LYG including 20 year projected benefits = £2,563
The cost per LYG including 30 year projected benefits = £2,074

These figures compare favourably with existing interventions and fall well below the commonly quoted £20,000 per LYG threshold.

3.6 Sensitivity of Cost per Life Year Gained in Non-Hodgkin's Lymphoma

The following graph shows the sensitivity of cost per LYG when considered against the cost of HDC. For the purpose of the sensitivity analysis, the clinical benefits have been restricted to those suggested by the trial data only; projections of benefit beyond the end of trial point have not been included.

Figure 13 Sensitivity of Cost per Life Year Gained in Non-Hodgkin's Lymphoma



Assuming the clinical benefits are as represented in the Parma trial, the cost-effectiveness of HDC remains below £20,000 even when the cost of a HDC treatment is increased to £20,000.

Consideration has also been given to a scenario where the clinical benefits are only half of those predicted in the study. In this case the cost per LYG rises to around £25,000.

The graph can also be used to estimate the cost-effectiveness if the five year projected benefits beyond the trial data are included. In this case a 2.3 LYG is predicted which would place the sensitivity line below all three lines shown on the graph. At this level of benefit the cost-effectiveness remains under £10,000 at the range of HDC marginal costs explored (£10-20,000).

3.7 Cost Benefit of High Dose Chemotherapy in Hodgkin's Disease

In considering the cost benefits of adopting HDC in relapsed and poor prognosis HD the overall survival benefits are compared with the implied marginal costs. The marginal survival benefit, as implied by the Linch trial data only, is considered first. This is, in effect, assuming that at the 54 month point the HDC cohort reduces immediately to the survival level of the standard chemotherapy treatment group. This is obviously pessimistic, but represents the data that are known and reported in the literature.

Table 13 Cost-effectiveness of High Dose Chemotherapy in Hodgkin's Disease: Trial Based Data

Cost-effectiveness Based on Trial Data Only (75 months)	Standard Chemotherapy	High Dose Therapy	Marginal Survival Analysis
Therapy Cost	£1,500	£15,600	£14,100
Survival (area under the estimate)	56 months	66 months	10 months
	4.7 LYG	5.5 LYG	0.8 LYG
Marginal Cost per LYG	-	-	£17,625

Based on this analysis it is predicted that HDC provides a marginal 0.8 LYG per patient at an increase in treatment cost of £14,100. This translates into a cost per LYG of £17,625.

Consideration can also be given to this analysis taking into account the predicted extended benefits based on the five year projection of ongoing treatment benefits. At the five year point the HDC group is reverted to standard chemotherapy survival levels. Under this scenario the marginal survival benefits increase to 1.6 LYG.

Table 14 Cost-effectiveness of High Dose Chemotherapy in Hodgkin's Disease: Extended Benefits Assumed

Benefit	Standard Chemotherapy	High Dose Therapy	Marginal Analysis
Therapy Cost	£1,500	£15,600	£14,100
Survival (area under the curve estimate)	64 months	92 months	28 months
	5.4 LYG	7.7 LYG	2.3 LYG
Marginal Cost per LYG	-	-	£6,130

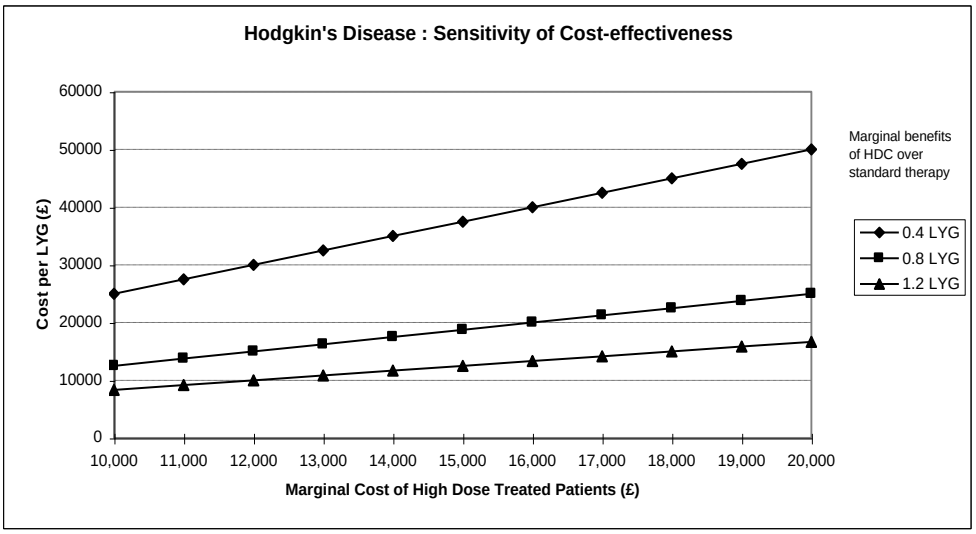
The cost per LYG including 5 year projected benefits = £6,130
The cost per LYG including 10 year projected benefits = £3,710
The cost per LYG including 20 year projected benefits = £2,170
The cost per LYG including 30 year projected benefits = £1,602

These figures compare favourably with existing interventions and fall below the commonly quoted £20,000 per LYG threshold.

3.8 Sensitivity of Cost per Life Year Gained in Hodgkin's Disease

The following graph shows the sensitivity of cost per LYG when considered against the marginal cost of HDC. For the purpose of the sensitivity analysis, the clinical benefits have been restricted to those suggested by the trial data only. Projections of benefit beyond the end of trial point have not been included.

Figure 14 Sensitivity of Cost per Life Year Gained in Hodgkin's Disease



Assuming the clinical benefits are as represented in the Linch trial, the cost-effectiveness of HDC remains below £20,000 until the costs of HDC treatment are increased to around £18,000.

Consideration has also been given to a scenario where the clinical benefits are only half of those predicted in the study. In this case the cost per LYG rises to around £30,000 at the current HDC marginal cost.

The graph can also be used to estimate the cost-effectiveness if the five year projected benefits beyond the trial data are included. In this case a 2.3 LYG is predicted which would

place the sensitivity line below all three lines shown on the graph. At this level of benefit the cost-effectiveness remains under £10,000 at the range of HDC marginal costs explored (£10-20,000).

4. OPTIONS FOR PURCHASERS AND PROVIDERS

The options for purchasers can be summarised as follows:

Option 1 *Do not support the use of High Dose Chemotherapy in the treatment of all lymphoma, even within the context of clinical trials.*

This is an extreme option and would really fly in the face of the strong clinical evidence of effectiveness in a number of the disease sub-groups of lymphoma. It would also deny the exploration of potential benefits in other sub-groups, indicated in phase II and observational/retrospective cohort studies.

Option 2 *Support the use of High Dose Chemotherapy within clinical trials only across all levels of lymphoma, both Non-Hodgkin's Lymphoma and Hodgkin's Disease.*

The case for the use of HDC with ABMT/PBSCT has certainly been strongly indicated in a number of lymphoma groups, establishing it as the therapy option of choice in patients with suitable functional status to tolerate HDC. However, there remain some areas where the benefits are very uncertain and remain speculative. An example of this would be low grade lymphoma and partial response high grade lymphoma.

Option 3 *Support the usage of HDC for lymphoma as suggested by the EBMT guidelines.*

The EBMT guidelines have been brought together to reflect the current state of treatment for lymphoma, and other malignancies, across Europe. It is expected that these guidelines will shortly become a strong measure by which centres will be expected to conform. The guidance recommends the use of treatment in a number of clear randomised controlled trials proven disease groups, whilst retaining a clinical trial basis for those where evidence is less clear cut.

Option 4 *Support the use of HDC for lymphoma as suggested in the clinical summary of the Guidance Note by the Trent Working Group on Acute Purchasing (i.e. include support for those areas felt to be proven ethically).*

In considering the EBMT guidelines together with their own clinical practice, the Trent Working Group on Acute Purchasing debated the relative merits of the guidelines. In the vast majority of cases the EBMT stance was confirmed with respect to clinical trial and recommended therapy. It was felt, however, that the case in high/intermediate grade lymphoma remained unproven other than in the clear evidence for use in relapsed patients. It was also felt that there were some specific disease types within low grade lymphoma which would never be subject to randomised trials.

Summary

It is the view of the clinical authors of this report that the most appropriate way forward is to support the use of HDC in those areas where trial evidence is clear cut and to continue support of clinical trials in those areas where benefits have been suggested from early trial data.

Within the context of the Trent Working Group, the invited clinicians discussed as a group the suggested EBMT guidelines. On the whole they considered their interpretation of the evidence to match with the EBMT position. There was slightly weaker support for a full recommended use in complete remission of high/intermediate grade lymphoma. A breakdown of the clinical view at the Trent seminar is provided alongside the EBMT recommendations in the evidence tables in Section 2.

Importantly, the Group felt that there were a number of specific prognosis and disease groups where the early trial data had been so convincing that the clinical views suggested no further supporting randomised controlled trial data would be produced for ethical reasons. In these cases, the clinicians suggested that support for treatment should be provided without such evidence. It would be particularly important in these groups to track outcomes for use in the retospective analysis of treatments.

5. DISCUSSION AND CONCLUSIONS

The use of HDC in the treatment of HD and NHL is already an established salvage therapy in certain prognostic groups. This Guidance Note helps to show the relative strengths and weaknesses of the trial and study evidence available in the public domain.

It is clear that there are some areas of lymphoma where the benefit of HDC still remains unproven. However, the strength of observational study evidence in some areas strongly supports the use of HDC, relapsed HD being a prime example.

The costs of HDC are partially offset by the reduced likelihood of follow-up chemotherapy following relapse, as patients often succumb to the disease relatively quickly. The pattern of second/third and even fourth line treatment is common in standard first line chemotherapy. Importantly, the economic arguments for HDC have been based on initial therapy costs only, excluding any longer-term benefits of HDC from reduced follow-up treatment.

The cost-effectiveness arguments for HDC in those areas of proven clinical efficacy, namely relapsed NHL and relapsed/partial response HD, hold firm even when tested under sensitivity analysis involving both costs and benefits. The cost-effectiveness ratios are certainly comparable with similarly supported therapies.

The recently published EBMT recommendations help to provide a framework with which to consider the role of HDC and are likely to become a set of European standards.

Finally, there also exists an ongoing HTA report, which considered the evidence for HDC in a range of cancers, including both HD and NHL. At the time of writing this report the HTA report is in the process of publication. However, a summary of its draft conclusions has been made available to the authors.

A summary of the draft HTA report findings is given below:

Intermediate/high grade Non-Hodgkin's Lymphoma

- The report concludes that, in the light of the current single Parma trial[11] evidence and with the lack of further ongoing trials, the use of HDC as a salvage therapy will be expected to continue as a standard therapy.

- As a direct first line therapy there is some evidence of effectiveness for the use of HDC, but not sufficient to determine the role as first line therapy.

- As a first line therapy consolidating a complete response to standard chemotherapy, there is some evidence of effectiveness with both survival and progression-free survival benefits indicated in a single trial. Ongoing trials are in progress looking at post remission treatment with HDC.

Low grade Non-Hodgkin's Lymphoma

- In low grade NHL there is no real trial evidence currently available to support its use.

Hodgkin's Disease

- The use of HDC is now regarded as standard salvage treatment in relapsed and refractory HD on the bases of the BNLI-Linch trial and the retrospective patient studies. The HTA considers the single trial to be too small on which to base firm conclusions. The report points towards an ongoing trial of HDC in relapsed patients (see appendix).

- The use of HDC in consolidating first remission is not currently supported by published trial evidence and should be considered only within clinical trial.

6. USE OF HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION: 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
High/Intermediate Non-Hodgkin's Lymphoma	Patients in first relapse, second and subsequent relapse	20-40 patients p.a. for a 'typical' health authority may be suitable for HDC treatment.	It is likely that patients who fail after HDC will not be re-challenged.	Recording of long-term survival rates.	Trial data suggest that an average of 1.1 LYG per patient is achievable against coventional chemotherapy.	Cost per LYG is suggested at £12,818 when using trial data only. Projecting benefits forward to 5 years reduces this value to £6,130 per LYG.
Low Grade Non-Hodgkin's Lymphoma	No patient groups currently indicated for HDC	20-30 patients p.a. for a typical health authority.				
Hodgkin's Disease	Patients in first, second and subsequent relapse	10 p.a. for a 'typical' health authority may be suitable for HDC treatment.	It is likely that patients who fail after HDC will not be re-challenged.	Recording of long-term survival rates.	Trial data suggest that an average of 0.8 LYG per patient is achievable against coventional chemotherapy.	Cost per LYG is suggested at £17,625 when using trial data only. Projecting benefits forward to 5 years reduces this value to £6,130 per LYG.

REFERENCES

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

2. The descriptive epidemiology of leukaemia and related conditions in parts of the United Kingdom 1984-1993. *Leukaemia Research Fund* 1997.

3. Appelbaum FR, Herzig GP, Ziegler JL, et al. Successful engraft of autologous bone marrow in patients with malignant lymphoma. *Blood* 1978; 52:85-92.

4. Philip T, Byron P, Maraninchi D, et al. Massive chemotherapy with autologous bone marrow transplantation in fifty cases of bad prognosis non-Hodgkin's lymphoma. *Br J Haematol* 1985; 60:559-609.

5. Pettengell R, Morgenstern GR, Woll PJ, et al. Peripheral blood progenitor cell transplantation in lymphoma and leukaemia using a single apharesis. *Blood* 1993; 12:3770-3777.

6. Schmitz N, Linch DC, Dreger P, et al. Filgrastim-mobilised peripheral blood progenitor cell transplantation in comparison with autologous bone marrow transplantation: Results of a randomised phase III trial in lymphoma patients. *Lancet* 1996; 347:353 - 357.

7. Smith TJ, Hillner BE, Schmitz N, et al. Economic analysis of a randomised clinical trial to compare filgrstim-mobilised peripheral blood progenitor cell transplantation and autologous bone marrow transplantation in patients with Hodgkin's and Non-Hodgkin's lymphoma. *J Clin Oncol* 1997; 15:5-10.

8. Hartmann O, Le Corroller AG, Blaise D, et al. Peripheral blood stem cell and bone marrow transplantation for solid tumours and lymphomas: hematologic recovery and costs. A randomised, controlled trial. *Ann Intern Med* 1997; 126:600-607.

9. Brugger W, Birken R, Bertz H, et al. Peripheral blood progenitor cells mobilised by chemotherapy plus granulocyte-colony-stimulating factor accelerate both neutrophil and platelet recovery after high dose V)-16, ifosfamide and cisplatin. *Br J Haematol* 1993; 84:402-407.

10. Gianni AM. Where do we stand with respect to the use of peripheral blood progenitor cells? *Ann Oncol* 1994; 5:781-784.

11. Philip T, Chauvin F, Armitage J, et al. Parma International Protocol: pilot study of DHAP followed by involved field radiotherapy and high dose chemotherapy with autologous bone marrow transplantation. *Blood* 1991; 77:1587-1592.

12. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma. *N Engl J Med* 1993; 328:1002-6.

13. Philip T, Gulglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemosensitive Non-Hodgkin's Lymphoma *N Engl J Med* 1995; 33 (23):1540-1545.

14. Phillip T, Hagenbeek A, Gomez F et al. Salvage treatment for chemotherapy resistant disease NHL: Review of 215 patients of the study and rationale for a second prospective study. *Ann Oncol* 1996; 7 suppl 3:054.

15. International Non-Hodgkin's Prognostic Factors Project. A predictive model for aggressive Non-Hodgkin's lymphoma. *N Engl J Med* 1993; 329:987.

16. Haioun C, Lepage E, Gisselbrecht C, et al. Comparison of autologous bone marrow transplantation with sequential chemotherapy for intermediate and high grade Non-Hodgkin's Lymphoma in first CR: a study of 464 patients, *J Clin Oncol* 1994; 12:2543-2551.

17. Haioun C, Lepage E, Gisselbrecht C, et al. Autologous bone marrow transplantation versus sequential chemotherapy for aggressive Non-Hodgkin's Lymphoma in first complete remission: A study of 541 patients (LNH 87-2 Protocol). *Ann Oncol* 1996; 7 suppl 3:A79.

18. Pettengell R, Radford J A, Morgenstern G R, et al. Survival benefit from high dose therapy with autologous blood progenitor cell transplantation in poor prognosis Non-Hodgkin's Lymphoma. *J Clin Oncol* 1996; 14:586-592.

19. Gisselbrecht C, Lepage E, Marel P, et al. Short and intensified treatment with autologous stem cell transplantation versus ACVB regimen in poor prognosis aggressive lymphoma Non-Hodgkin's Lymphoma 93-3 protocol. *Bone Marrow Transplant* 1996; 19 suppl 1:5153.

20. Gianni A, Bregni M, Siena S, et al. High Dose Chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. *N Engl J Med* 1997; 336:1290-1297.

21. Martelli M, Vignetti M, Zinzani PL, et al. High dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin and cytarabine in aggressive Non-Hodgkin's Lymphoma with a partial response to front-line chemotherapy: A prospective randomised Italian multi-centre study. *J Clin Oncol* 1996; 14:534-542.

22. Verdonck LF, van Putten WL, Hagenbeck A, et al. Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive Non-Hodgkin's Lymphoma. *N Engl J Med* 1995; 332:1045-1051.

23. Prince HM, Crump M, Imrie K, et al. Intense therapy and autologous transplantation for patients with an incomplete response to front-line therapy for lymphoma. *Ann Oncol* 1996; 1043-1049.

24. Weisdorf DJ, Anderson JW, Glick JH, et al. Survival after relapse of Low Grade Non-Hodgkin's Lymphoma: Implications for Marrow Transplantation. *J Clin Oncol* 1992; 10:942-947.

25. Chopra R, Goldstone AH, Pearce R, et al. Autologous versus allogeneic bone marrow transplantation for Non-Hodgkin's Lymphoma: A case-controlled analysis of the European Bone Marrow Transplant Registry data. *J Clin Oncol* 1992; 10:1690-1695.

26. Jost LM, Jacky E, Dommann-Scherrer C, et al. Short term weekly chemotherapy followed by High Dose Chemotherapy with autologous bone marrow transplantation for lymphoblastic lymphoma in adult patients. *Ann Oncol* 1995; 6:445-451.

27. Verdonck LF, Dekker AW, de Gast GC, et al. Autologous bone marrow transplantation for adult poor risk lymphoblastic lymphoma in first remission. *J Clin Oncol* 1992, 10: 644-646.

28. Baro J, Richard C, Sierra J, et al. Autologous bone marrow transplantation in 22 patients with lymphoblastic lymphoma responsive to conventional dose chemotherapy. *Bone Marrow Transplant* 1992; 10:33-38.

29. Longo DL, Duffy PL, Young RC, et al. Conventional dose salvage combination chemotherapy in patients relapsing with Hodgkin's Disease after combination chemotherapy: the low probability of cure. *J Clin Oncol* 1992; 10:210-218.

30. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone marrow transplantation in relapsed and resistant Hodgkin's Disease: results of a BNLI randomised trial. *Lancet* 1993, 341: 1051-1054.

31. Chopra R, McMillan AR, Linch DC, et al. The place of high dose BEAM therapy with autologous bone marrow transplantation in poor risk Hodgkin's Disease: A single centre 8 year study of 155 patients. *Blood* 1993; 81: 1137-1145.

32. Gianni AM, Siena S, Bregni M, et al. High dose sequential chemo radiotherapy with Peripheral Blood Progenitor Cell support for relapsed or refractory Hodgkin's Disease-6 year update. *Ann Oncol* 1993; 4:889-891.

33. Schmitz N, Glass B, Dreger P, et al. High dose chemotherapy & hematopoietic stem cell rescue in patients with relapsed Hodgkin's Disease. *Ann Haematol* 1993; 66:251-256.

34. Armitage JO, Bierman PJ, Vose JM, et al. Autologous bone marrow transplantation for patients with relapsed Hodgkin's Disease. *Am J Med* 1991; 91:605-611.

35. Fermé C, Bastion Y, Lepage E, et al. The MINE regimens as intensive salvage chemotherapy for relapsed and refractory Hodgkin's Disease. *Ann Oncol* 1995; 6:543-549.

36. Reece DE, Barnett MJ, Connors JM, et al. Intensive chemotherapy with Cyclophosphamide, Carmustine and Etoposide followed by autologous bone marrow transplantation for relapsed Hodgkin's Disease. *J Clin Oncol* 1991; 9:1871-1879.

37. Andre M, Henryamar M, Pico JL, et al. Autologous stem cell transplantation improves survival of refractory Hodgkin's patients: A retrospective match-controlled study. *Br J Haematol* 1996; 93:547.

38. Sweetnam J. High dose therapy in autologous bone marrow transplantation for adult patients with primary-refractory Hodgkin's Disease 30% of patients are progression free at 5 years: data from 290 patients reported to the EBMT. (Personal Communication).

39. Reece DE, Barnett MJ, Shepherd DJ, et al. High dose cyclophosphamide, carmustine and etoposide with or without cisplatin and autologous transplantation for patients with Hodgkin's Disease who fail to enter a complete remission after combination chemotherapy. *Blood* 1995; 86:451-456.

40. Hasenclever Dand Diehl V. A numerical index to predict tumour control in advanced Hodgkin's Disease. *Blood* 1996; 88:673a.

41. Bierman PJ, Bagin RG, Jagannath S, et al. High-dose chemotherapy with autologous haematopoietic rescue for Hodgkin's Disease following first relapse after chemotherapy. *J Clin Oncol* 1993; 12:366.

42. Chopra R, Goldstone AH, Pearce R, et al. Autologous versus allogeneic bone marrow transplantation for NHL: A case-controlled analysis of the EBMT registry data. *J Clin Oncol* 1992; 10:1690-1695.

43. Jones RJ, Ambinder RF, Piantadosi S, et al. Evidence of graft versus lymphoma effect associated with allogenic bone marrow transplantation. *Blood* 1991; 77:649.

44. Rohatiner AZ, Freedman A, Nadler L, et al. Myeloablative therapy with ABMT as consolidation therapy for recurrent follicular lymphoma. *J Clin Oncol* 1994; 12:1177-115.

APPENDIX ONGOING TRIALS OF HIGH DOSE CHEMOTHERAPY IN NON-HODGKIN'S LYMPHOMA/HODGKIN'S DISEASE

HDC in Non-Hodgkin's Lymphoma

			Treatment regimens		
Trial code	**Status**	**Disease Eligibility**	**A**	**B**	**Planned Accrual**
EORTC-20901*	Open	Adult intermediate-and high-grade Non-Hodgkin's Lymphoma	ADR, TENI, CTX, PRED, VCR, BLEO **HDT + ABMT/PBSC** BCNU, ETOP, CYT, CTX Radiotherapy	ADR, TENI, CTX, PRED, VCR, BLEO radiotherapy	300
Scottish Lymphoma Group NHL V(a)	Open	High grade malignant lymphoma (good index)	CHOP or VAPEC B **HDT + PBSC** L-PAM	CTX, ADR, VCR, PRED or ADR, CTX, VCR, BLM, ETOP, PRED	51 patients entered to date
EORTC - 20963* BNLI Hovon 35	Open	Stages 11 or IV follicular Non-Hodgkin's Lymphoma	Induction therapy **HDT + APBSC** CTX, TBI Interferon maintenance	Induction therapy Interferon maintenance	469
LY02 UKLG/ANZLG/EBMT	Open	Poor risk intermediate/high grade Non-Hodgkin's Lymphoma	**HDT + ABMT**	CTX, ADR, VCR, PRED	500
EBMT-ECUP	Closed (30/04/97)	Adult relapsed Follicular Non-Hodgkin's Lymphoma	CTX, ADR, VCR, PRED **HDT + ABMT/PBSC** CTX, TBI	CTX, ADR, VCR, PRED	200
UKLG-LY01	Closed (30/04/97)	Adult Lymphoblastic Lymphoma	VCR,ADR,CTX,ASP PRED, MTX, DNR, CYT, or CTX,ADR,VCR,PRED, ASP, MTX, Radiotherapy **HDT + ABMT/PBSC** CTX,TBI or BCNU,ETOP,CTX l-PAM	VCR,ADR,CTX,ASP, PRED, MTX, DNR, CYT, or CTX,ADR,VCR,PRED,ASP, MTX, Radiotherapy Maintenance	200
NCI-D78-017-142*	closed (01/01/81)	Non-Hodgkin's Lymphoma	**HDT + ABMT/AIBMT** ADR, CTX, TBI MTX, CYT, TG, MTX or DAC, VCR	ADR, CTX MTX, CYT, TG, MTX or DAC, VCR.	28

			Treatment regimens		
Trial code	**Status**	**Disease Eligibility**	**A**	**B**	**Planned Accrual**
DUT-KWF-CKVO-8518*	Closed (01/01/93)	Intermediate - and high-grade Non-Hodgkin's Lymphoma	CTX, ADR, VCR, PRED **HDT + ABMT** CTX, TBI	CTX, ADR, VCR, PRED	240
MSKCC-89084* NCI-V89-0192	Closed (12/01/93)	Advanced low-grade Non-Hodgkin's Lymphoma	PRED,MTX,ADR,CTX,ETOP NM, VCR, PCZ, PRED **HDT + ABMT** CTX,ETOP, TBI	PRED,MTX,ADR,CTX,ETOP NM, VCR, PCZ, PRED Radiotherapy	106
				maximum planned accrual	2,785

Source : Draft HTA report : Bone Marrow & Peripheral Blood Stem-cell Transplantation for Malignancy

* PDZ trial reference code

Shaded boxes indicate open UK based and EORTC trials.

HDC in Hodgkin's Disease

Trial Code	**Disease Eligibility**	**HDT**	**CC**	**Planned Accrual**
HD01 (EBMT and German Hodgkin's Disease Study Group)	Relapsed disease, responding to chemotherapy	HDT + ASCT	ADR,BLEO,VBL,DAC or other standard regimen	146
EBMT Lymphoma working party	First complete or good partial remission in poor prognosis patients	**HDT + ASCT**	-	-
HD3 Scottish and Newcastle Lymphoma Group	First complete remission in "poor prognosis" Hodgkin's Disease,	**HDT + ABMT** L-PAM, ETOP	VCR, ETOP, PCZ, CHL, ADR,BLM, PRED	150
			Maximum Planned Accrual	>296

Source : Draft HTA report : Bone Marrow & Peripheral Blood Stem-cell Transplantation for Malignancy

Shaded boxes indicate UK based and EBMT trials.

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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E-mail scharrlib@sheffield.ac.uk

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