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Role of High-Dose Chemotherapy and Autologous Bone Marrow Transplantation in the Treatment of Lymphoma

Thierry Philip and Pierre Biron

INTRODUCTION

EVEN THOUGH malignant lymphomas can be considered among the most sensitive of malignancies as regards response to chemotherapy and radiation therapy, there still exists a significant fraction of adult patients for whom intensive therapy and bone marrow transplantation (BMT) can be discussed. Advances in the area of bone marrow transplantation have been associated with numerous reports of very promising pilot studies [1]. However, no clear indication based on a randomised study is found in the world literature. The purpose of this review is to define the optimal timing for autologous bone marrow transplantation (ABMT) in intermediate and high grade non-Hodgkin lymphomas (NHL).

50 cases of diffuse NHL are observed every year for a population of 1 million adults [2]. 20 of them are observed in patients over 60 years old at diagnosis and 10 are localised at time of first symptoms. Thus only 20 diffuse NHL/year/1 million adults can be considered for bone marrow transplantation. Even with restricted indications, as many as 7/year/1 million can be considered for BMT in first complete remission, 2/year/1 million for BMT in first partial remission, 4/year/1 million for BMT in sensitive relapses, 2/year/1 million for BMT in non-explosive resistant relapses and possibly also an additional 2/year/1 million adults for primary refractory patients. A total of 17 BMT/year/1 million adults will mean between 300 and 500 indications in France and between 1200 and 2000 indications in the USA [1, 2]. As a comparison, only 700 BMT for lymphomas were recorded in the world betwen 1981 and 1985 and only 500 autologous bone marrow transplantations were performed in France in 1987 (the highest number of ABMTs in one single country in Europe) [2]. The necessity to clearly define indications for BMT in this disease is therefore clear and could be considered as a priority for public health in developed countries.

Correspondence to T. Philip.
The authors are at the Centre Léon Bérard Bone Marrow Transplant Department, 28 rue Laënnec, 69373 Lyon Cedex 08, France.
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TIMING FOR ABMT

What is optimum timing for ABMT in CR1 for intermediate-grade and high-grade lymphomas? The optimum timing for ABMT in Burkitt's lymphomas has been extensively reviewed [3,4]. For lymphoblastic lymphomas it is in fact comparable to lymphoblastic leukaemia. However, intermediate grade lymphomas, according to the International classification, are the most common NHL in adults [5]. The majority of reported regimens are able to produce 60% long term survival in this group [6]. It is important to consider therefore that 10% of the patients will never reach first CR and will progress on induction therapy, that 8% will only be in partial response after induction and that approximately 8% will die early of toxicity [6]. If these patients and patients over 60 years old at diagnosis are excluded, survival curves of 70–75% are common and indications for BMT very unsecure.

The selection of bad prognosis groups is thus mandatory if BMT is considered in first CR. It is now widely accepted that candidates for prospective studies can be defined as patients less than 55 years old at diagnosis, with at least 2 extranodal localisations or a tumour of at least 10 cm at diagnosis, with a bad Karnofsky score (< 70%) or with bone marrow or CNS disease at initial presentation [6]. This group is reported to have an expected survival with conventional regimen of 55% at 3 years (B. Coiffier, Centre Hospitalier Lyon). Only prospective and randomised studies are acceptable in this field. They should avoid protocols with high toxic death rates and they should include at least 150 patients in each arm. The European NHL group is currently studying this group of patients in a randomised multi-institutional European trial (C. Gisselbretch, chairman).

ABMT IN PRIMARY REFRACTORY PATIENTS

The term refractory lymphoma has frequently been utilised in an ambiguous context and thus needs to be better defined. In describing the results of salvage studies, the frequently used statement "patients who have failed front line regimens" is not appropriate. The setting in which these patients "failed" is much more important than the fact they failed. Those patients who fail to achieve a major response to front line chemotherapy regimens are without doubt the best example of refractory disease.

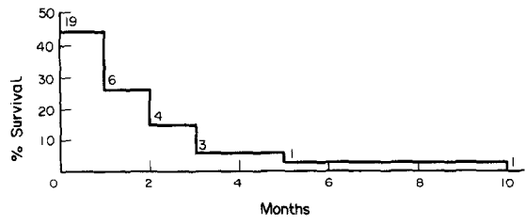

Fig. 1. 34 patients with primary refractory NHL [1].

As shown in Fig. 1, 34 such primary refractory patients were reported in 1987 from major BMT centres in the world [1]. These 34 patients who never entered complete remission in the course of their disease underwent transplantation while their disease was progressing during conventional or salvage therapy. 2 patients died early, before their response could be assessed, and they were excluded from evaluation. 24 of the remaining 32 responded to high-dose therapy (9 had a complete response, 15 a partial response, and 8 no response; response rate, 75%), confirming the dose-response effect even in patients with highly resistant disease. However, the median duration of response was only 160 days, and no patient was alive and free of disease at three years (Fig. 1). In 1991, these patients will not be cured with BMT and despite their very high response rate they are not good candidates for this procedure. Thus there is no indication for ABMT in primary refractory patients except in prospective experimental studies.

BMT IN NON-HODGKIN LYMPHOMAS

Partial responders to first-line induction therapy are chemosensitive high-risk patients. This is probably the best indication for BMT in NHL. The best reported results in the world literature in PR after induction are Coiffier's with 27% survival (B. Coiffier). Investigators using M-BACOD as induction treatment have reported 14% of partially responding patients alive at 2 years and for those treated with ProMACE-MOPP, 15% survival at 30 months. Before undertaking treatment for partial responding lymphoma, it is mandatory to establish as certainly as possible the presence of residual active disease [7]. An effort to obtain tissue to establish the presence of tumour should be a prerequisite.

As shown in Fig. 2 and as reported with Hartmann, pilot studies with ABMT were able to report 71% disease free survival at 90 months for a group of 17 patients, all with proven active lymphomas at time of BMT. These preliminary results should be confirmed, but BMT can be strongly recommended in 1991 for these patients if a biopsy shows active lymphomas after 4 course of a conventional induction regimen [7].

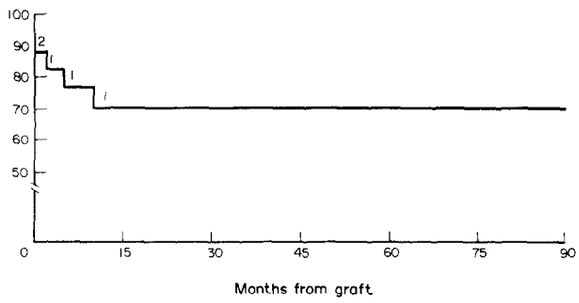

Fig. 2. Event free survival in NML patients in partial response after ABMT.

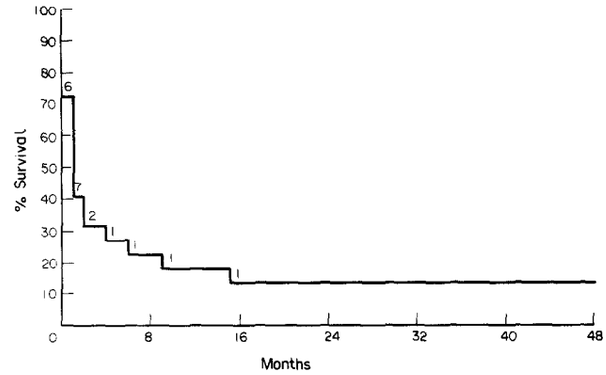

Fig. 3. 22 resistant relapses [1].

ABMT IN RELAPSES OF NHL

This group of patients was extensively reviewed previously by our group [1,5,6]. In summary, two distinct situations are observed.

Patients who previously reached CR1 on conventional therapy and then relapsed, and who are not responding to conventional rescue protocols are called resistant relapses. 22 of such patients were reported in 1987, as shown in Fig. 3. Response rate was good (i.e. 59%) with quite high CR rate (45%). However, survival for this group is poor (15%) and should be improved. Considering an individual progressing at relapse under conventional therapy, BMT is probably the only chance of cure and can be highly recommended. An improvement of these results can be expected with the use of biological response modifiers immediately after transplantation.

Patients who previously reached CR1 on conventional therapy and then relapsed and who are still responding to conventional rescue protocols are called sensitive relapses [1]. As shown in Fig. 4 , 43% are in CR2 at time of BMT and 86% of the others are transformed to CR2 with the conditioning regimen, 40% of these patients are long term survivors after BMT, with a price of 20% toxic death [1]. Reports of 20% survival at 2 years in this group without BMT [5] (B. Coiffier) as well as a high prevalence of this group in ABMT reported pilot studies have together led to increasing uncertainty about the appropriate selection of patient for ABMT [6]. A randomised study (i.e. Parma protocol) is currently aiming to answer the question of the role of BMT in this group of patients.

In conclusion, sensitive relapses are probably very good

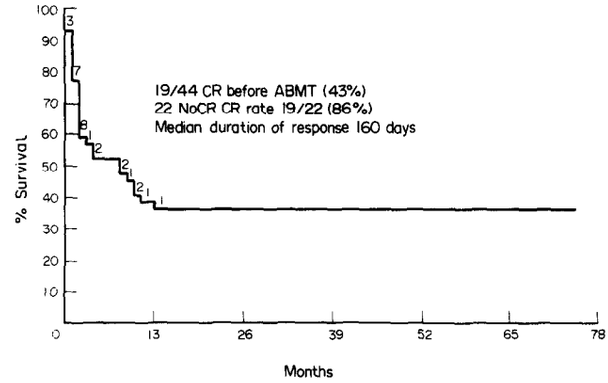

Fig. 4. 44 sensitive relapses.

indications for BMT but randomised studies are needed to show whether BMT is the best available strategy for this group of patients.

CONCLUSIONS AND PROSPECTIVES

Indications for BMT in non Hodgkin lymphomas as reviewed in this paper can lead to 2000 or 3000 BMT every year in the USA. Randomised studies are needed to convince the medical community and also . . . insurance companies. In December 1990:

— Randomised studies are necessary and welcome. They should all be considered as high priority.

— PR with positive biopsy and sensitive relapses are the only group of patients in which BMT may be the best therapy available for diffuse lymphomas, despite the lack of proof with prospective studies.

— Primary refractory patients and resistant relapses are not good indications and should be a group eligible for phase II studies.

— Non-randomised studies in CR1 are probably unethical and certainly unwise.

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Current Controversies in the Management of Testicular Cancer

A. Horwich

INTRODUCTION

TESTICULAR CANCER is important to oncology not only as a model of a curable tumour, but also because of the relatively young age of presentation, the rising incidence, the expression of sensitive and relatively specific tumour markers and the contribution of the high proportion of surviving patients to knowledge of late treatment toxicity. The vast majority of both seminomatous and non-seminomatous tumours are associated with carcinoma *in situ* (CIS) of the testis, a lesion also found in 0.5%–1.0% of infertile men, 5% of contralateral testes in patients with testicular germ cell tumours, 50% of extragonadal germ cell tumour presentations and nearly all cases of gonadal dysgenesis [1]. Follow-up has suggested that CIS progresses to invasive tumour at a rate of approximately 50% of cases within 5 years [2], forming either seminoma or non-seminoma. Carcinoma *in situ* is an aneuploid lesion and seminoma has a modal chromosome number of 60–69, non-seminoma 50–59 and combined tumours a number in between these two [3, 4].

The great majority of germ cell tumours have an isochromosome of the short arm of chromosome 12 [5]. The Kirsten *RAS* oncogene is on chromosome 12p and the formation of the isochromosome thus amplifies c-Kirsten-*RAS*. However, the relevance of this to prognosis is unclear. Non-seminomatous tumours also have a high frequency of chromosome 1 abnormalities [3, 6].

MANAGEMENT OF CIS

This premalignant lesion is found in approximately 5% of contralateral testes sampled at the time of orchidectomy for germ cell tumour [2]. The incidence of CIS is increased in patients with an atrophic contralateral testis or in patients with a history of testicular maldescent. The fact that 50% of CIS lesions progress to invasive tumour within 5 years has led to the advocacy of routine contralateral testicular biopsy to diagnose CIS [7]. An alternative approach is to consider biopsy only in patients with one of the predisposing risk factors.

Once CIS of the contralateral testis is diagnosed, options for management include observation, orchidectomy, or low dose testicular radiation. Preliminary evidence would suggest that long-term control of CIS by systemic chemotherapy is uncertain [8]. In the past, this lesion has not been diagnosed and thus the contralateral testis has, of necessity, been managed by observation. 2–5% of patients do develop a new germ cell tumour of the contralateral testis, however, the excellent prognosis of

Correspondence to A. Horwich, Royal Marsden Hospital and Institute of Cancer Research, Downs Road, Sutton, Surrey SM2 5PT, U.K.
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