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The Importance of Dose: Lymphomas as a Model of Chemosensitive Malignancies

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Chemotherapy dose intensity is probably important to the success of treatment for some human malignancies. Recombinant human haemopoietic growth factors have recently become available to clinicians to ameliorate the myelosuppression that follows cytotoxic chemotherapy. Their use to increase the dose intensity of treatment, either by simply allowing the administration of the planned dose on schedule or by increasing the dose or dose rate above the conventional ones, is being actively investigated by several European and American groups. In several reported studies, neutropenia is no longer dose limiting when granulocyte colony-stimulating factor is used to help to intensify cytotoxic chemotherapy, but thrombocytopenia or mucositis are. The use of circulating haemopoietic progenitor cells, released into the blood stream by growth factors and infused with or without autologous bone marrow, has been reported to consistently reduce the overall period and severity of thrombocytopenia following intensive chemotherapy in patients without pre-existing severe bone marrow damage. However, no clear improvements in survival have yet been documented with the use of these techniques. Difficulties in study design include a number of variables potentially involved (tumour model, patient population, adjuvant or advanced disease, dose of cytotoxics, intervals, end-points, etc.), and there is clearly a need for more studies and longer follow-up. Lymphomas, both non-Hodgkin and Hodgkin's disease, are the prototypes of chemosensitive malignancies curable by chemotherapy alone even in disseminated disease. Therefore, they would seem to be adequate models to test the dose intensity hypothesis in the clinic. However, there are important differences between these two types of disorder. The success of conventional therapies in these conditions suggests that further improvements in outcome and long-term survival by further increases in dose intensity with current drugs will require careful study designs, due attention to prognostic factors, and reasonable expectations.
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INTRODUCTION

IN SEVERAL experimental systems, particularly animals with rapidly growing tumours such as the L1210 leukaemia, cure rate is often sacrificed if dose intensity is decreased [1]. However, in clinical practice, doses of chemotherapy are often reduced or cycles delayed in deference to the toxic sequelae of treatment; particularly as a consequence of neutropenia. Reductions in dose rates often result in minimal decreases in toxicity, while altering the therapeutic response rate and hence success of treatment. This is one of the reasons why the recent introduction of recombinant human haemopoietic growth factors in clinical practice has been welcomed.

Recombinant human haemopoietic growth factors have recently become available to clinicians to ameliorate the myelosuppression that follows cytotoxic chemotherapy [2, 3]. The administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF, filgrastim) to prevent neutropenia and neutropenic fever in patients treated with semi-intensive chemotherapy regimens for small cell lung cancer, has been shown in two large randomised placebo controlled studies in the U.S.A. and Europe to reduce the number of infectious complications and to allow the administration of most chemotherapy cycles without dose reductions or dose delays [4, 5]. However, the relative increase in dose intensity of chemotherapy in this tumour model has not yet been shown to improve outcome and survival. Lymphomas, both non-Hodgkin and Hodgkin's disease, are the prototypes of chemosensitive malignancies curable by chemotherapy alone even in disseminated disease. Therefore, they would seem to be adequate models upon which to test the dose intensity hypothesis in the clinic [6]. However, there are important differences between these two types of disorder. Here, we will review some of these differences and some of the most representative retrospective and prospective data on the importance of dose in the management of lymphomas, with particular emphasis on the use of recombinant colony-stimulating factors.

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HODGKIN'S DISEASE

One of the advantages of the Hodgkin's disease model, as compared with the non-Hodgkin, is the fact that there is wide consensus on the utility and applicability of the Ann Arbor staging and the Rye classification of histopathological groups (Tables 1 and 2). In what is probably the first instance of the "curability" of a malignant condition by chemotherapy alone even in the presence of disseminated disease, De Vita *et al.* [7] reported in 1980 on some 200 patients with Hodgkin's disease treated with nitrogen mustard, vincristine, procarbazine, prednisone (MOPP) and followed for 10 years: the complete response rate (CR) was 80%, and 68% of the complete responders remained disease-free for more than 5 years. But in another interesting study, it took Huguley *et al.* more than 100 patients and 5 years follow-up to prove that the standard combination

Table 1. Relative advantages of Hodgkin's disease as a model

(1) Good staging system (Ann Arbor Staging).
(2) Valid and reproducible pathological nomenclature (Rye classification).
(3) Generally, patients who relapse after being off treatment for over 1 year have an excellent chance of achieving a second CR with the same induction regimen.
(4) Relapse beyond 1 year of discontinuing treatment is less frequent in the intermediate and high-grade malignant lymphomas than in Hodgkin's disease.
(5) Retreatment with the same induction regimen is not as feasible for non-Hodgkin lymphomas in view of the fact that most of these patients have received the maximum cumulative dose of doxorubicin during induction.

Table 2. Relative disadvantages of high-grade non-Hodgkin lymphoma as a model

(1) Ann Arbor Staging system no longer considered to be adequate.
(2) At least seven pathological classifications have been used in international studies: Rappaport, Lukes and Collins, Kiel, British National Lymphoma, Dorfman, WHO classification, Working Formulation.
(3) Several prognostic factors (age, bulky disease, serum LDH, beta-2-microglobulin, Ann Arbor stage IVB, performance status) are widely accepted and should be used to stratify patients.
(4) Some 12 combination chemotherapies are commonly employed worldwide, but none is clearly superior to the standard CHOP chemotherapy.

chemotherapy regimen MOPP is indeed superior to nitrogen mustard alone [8].

However, the patient who fails to achieve a CR on front-line therapy (and whose maximum response is only a partial remission) has no chance for cure by continuing the initial regimen and should be considered to have refractory disease. In the past, most clinicians continued the same type of therapy until there was clear evidence of progressive disease; but evidence is accumulating to show that if after three to six courses of chemotherapy a plateau is reached, the patients's disease should be considered refractory and the treatment should be changed to a non-cross-resistant regimen to induce a CR [9]. Often, the quality of the response to front-line therapy is one of the most important variables in predicting response to salvage therapy. However, unlike drug-resistant refractory non-Hodgkin lymphoma, it is a general observation that patients with refractory or relapsed Hodgkin's disease, unresponsive to conventional therapy, may still respond and have durable remissions with high-dose therapy and autologous bone marrow support, although survival at 2 years may be less than 30% and high-dose therapy undoubtedly carries a substantial risk in this population of heavily pretreated patients [10].

A comparison of studies of MOPP chemotherapy for Hodgkin's disease at different centres shows variability in treatment outcome. Although response rates were similar, the more important parameter of relapse-free survival varied markedly, being 55% at 15 years in the NCI series [7], but only 36% at 8 years in Milan [11] and 31% at 5 years in the SWOG studies [12]. Prognostic variables in the different groups of patients do not appear to explain the different outcome. However, a striking difference is apparent in the amount of chemotherapy given in different centres.

In order to try to explain the differences in survival between groups of patients treated at different centres, De Vita *et al.* calculated the relative dose intensity of chemotherapy from the different centres and correlated it with complete remission rates and disease-free survival [13]. There was a retrospective trend for a more favourable outcome for patients receiving MOPP at a greater dose intensity. The correlation was even more striking when comparisons could be made with actual RDI (amount of chemotherapy actually given rather than planned doses). Reductions of 29% and 38% in the ECOG and Milan studies, respectively, resulted in 33% and 35% decreases in overall disease-free survival.

A similar retrospective analysis of experience at Stanford (U.S.A.) revealed that the dose rate and total dose of mustine, vincristine and procarbazine were significantly correlated with complete remission rate, particularly in patients with B symptoms [14]. Patients receiving <65% of the projected dose of mustine had a significantly poorer survival than those receiving >65%. The NCI performed a multivariate analysis on patients treated with MOPP and found that the dose of vincristine correlated significantly with outcome [15].

Trials of MOPP or doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy in comparison with alternating MOPP–ABVD failed to demonstrate a significant advantage for alternating chemotherapy, but did reveal that dose reductions in patients receiving MOPP resulted in poorer treatment outcome [16]. For example, in the Milan trial 35% of patients experienced a 50% reduction of the dose of vincristine, and in 9% of patients vincristine was permanently discontinued because of toxicity. In this study 50% of patients in the MOPP arm experienced relapse in the first 24 months compared with only 34% of patients at the NCI over a 14-year follow-up [17]. As well as showing the dangers of inadequate dosing, these results illustrate that dose modification is carried out even in major medical centres. Data clearly supported the concept of dose intensity in Hodgkin's disease and argue strongly against unnecessary dose reductions or delays.

Coldman and Goldie [18], on a recent reassessment of their 1979 mathematical model for relating the drug sensitivity of tumours to their spontaneous mutation rate, suggest that the likelihood of therapeutic success depends on the probability that there are no resistant tumour cells and the probability that all the sensitive cells are eliminated (which may not occur if insufficient therapy is administered). In consequence, an early introduction of intensive high-dose therapy (with some form of bone marrow support), particularly in patients whose prognosis appears to be poor *a priori*, should lead to better therapeutic results. However, in a condition like Hodgkin's disease where second line (or even third line) therapy can often salvage the patient, the use of very high dose therapy with autologous bone marrow support (ABMT) in poor risk patients to consolidate a first remission remains highly controversial but is being investigated by several groups.

Carella *et al.* [19] have recently described the use of autologous bone marrow transplantation (ABMT) as adjuvant treatment for high-risk Hodgkin's disease in first complete remission after MOPP/ABVD protocol. Although it was not a randomised study, and patient numbers are still small, results are encouraging. The "very poor prognosis" group considered to be suitable for ABMT was defined as: age < 60 years, B symptoms, stage IV with > 1 extra nodal site plus: marrow involvement (low

haematocrit); lactate dehydrogenase (LDH) > 400; erythrocyte sedimentation rate (ESR) > 50; lymphocyte count < 0.75 (relative lymphopenia). According to this Italian group, patients with high bulk stage IVB disease, > 30 years of age, pulmonary involvement, at least one extra-nodal site and a high serum LDH have only a 30% chance of relapse-free survival even after achieving a CR. 15 patients with very poor prognosis Hodgkin's disease in remission after MOPP/ABVD regimen were treated with high-dose chemotherapy and ABMT immediately after achieving a CR. 13 patients (86.6%) remained alive and in CR at a median time of 36 months (range 10–64 months) post-transplant. In the other 2 patients reasons for failure included relapse of Hodgkin's disease (1 patient) and death due to interstitial pneumonitis probably secondary to carmustine therapy. These patients were compared with a historical control group consisting of 24 patients with the same poor prognostic factors, who achieved CR with MOPP/ABVD and did not receive other treatment. 8 of 24 patients (33%) remain alive and in CR at a median time of 42 months (range 19–83 months). It was concluded that early sequential treatment of a highly effective drug combination (MOPP/ABVD given sequentially rather than alternating) combined with high-dose therapy and ABMT can substantially improve the likelihood of cure in these advanced stage very poor prognosis Hodgkin's disease patients. However, these conclusions have been criticised on several grounds [20]. Thus, other groups have concluded that stage IV Hodgkin's disease is a relatively homogeneous prognostic group, and, in any case, the specific group of stage IV patients described by Carella *et al.* is fortunately very rare. Randomised trials will need to be undertaken, but a consensus should first be achieved on the correct group of high risk patients.

One of the main arguments for not using these type of aggressive therapies has traditionally been the very high haematological and non-haematological toxicity associated with them, which often resulted in 10–20% of iatrogenic deaths. The introduction of haematopoietic growth factors to speed up recovery following ABMT, and the judicious use of growth factor-primed circulating progenitor cells has led to a marked decrease in haematological toxicity and infectious complications [21, 22]. Following an initial report by Socinski *et al.* [23], who described 18-fold increases in the numbers of circulating myeloid progenitors (GM-CFUs) after chemotherapy alone and up to 60-fold rises when GM-CSF was added, Gianni *et al.* [24] described the harvesting by leucapheresis of circulating progenitor cells following high-dose cyclophosphamide and GM-CSF, and their use to speed up bone marrow recovery. The most useful contribution of circulating progenitors is probably the sparing effect on platelet transfusions: in a study reported by Sheridan *et al.* [25], autologous circulating progenitor cells collected during the continuous subcutaneous infusion of G-CSF (filgrastim) alone (without chemotherapy) drastically reduced platelet recovery time in patients treated with high-dose chemotherapy (cyclophosphamide and busulphan) and ABMT. While we wait for a putative recombinant human haematopoietic growth factor selective for megakaryocyte proliferation and differentiation, circulating progenitor cells are a valid therapeutic technique, although their specific indications need to be better defined. The absence of suitable platelet donors, the development of anti-platelet antibodies or the presence of bone marrow infiltration by tumour cells might be potential indications, although it seems that circulating tumour cells are not uncommon contaminants of leucapheresis products [26].

In conclusion, clinical evidence so far shows that dose and dose intensity are important determinants of treatment outcome in Hodgkin's disease.

Table 3. Why is there no optimal single treatment regimen for high-grade NHL?

1. Use of historical controls or of single institutions' data.
2. Heterogeneity of patient prognostic factors.
3. New regimens are often not confirmed by large multicentric prospective studies.
4. When these larger confirmatory trials take place, results (disease-free interval, complete response rates and survival) are often not so good as original reports.
5. Late relapses and chronic toxicities of new regimens are largely unpublished.

NON-HODGKIN LYMPHOMA

There are several reasons why there is still no single treatment universally applicable to patients with high grade non-Hodgkin lymphoma (NHL). Some of the main reasons are summarised in Table 3. This lack of consensus is partly why several leaders in the field have opted for the "back to the blackboard approach" and have produced a critical review on therapeutic results, and a consensus on independent prognostic factors [27]. The main results of a consensus of 16 cooperative groups or single institutions in Europe, Canada and the U.S.A., after careful reviewing of 3273 patients with stage I–IV diffuse, mixed, large cell, or immunoblastic lymphoma (treated with intensive combination chemotherapy between 1982 and 1987) are summarised in Table 4. It can be sobering to realise that in spite of the widely held belief that high grade NHL is essentially a curable condition, the 5-year overall survival figure of about 50% does not differ greatly from the same figure for breast carcinoma patients with positive axillary nodes at presentation, by many thought to be an essentially incurable condition until recently. Because there is also lack of consensus among pathologists regarding the histopathological classification of lymphomas (clearly a basic requirement for any logical interpretation of therapeutic results), international clinico-pathological projects are also in progress [28], and opinion leaders are working on a new staging classification. However, it appears likely that with the emergence of new pathological entities (or subtypes) as defined by new monoclonal antibodies and DNA markers, the global picture will become more complex before it becomes more simple.

Table 4. International predictive model for aggressive lymphomas (presented at ASCO, 1992)

(A) Therapeutic overall results
- CR rate : 65%
- 2-year survival: 64%
- 5-year survival: 52%

(B) Independent prognostic factors
- Age (less or more than 60 years)
- Stage (I/II versus III/IV)
- Number of extranodal sites (less versus more than one)
- Performance status (ECOG less than 2 or more than 2)
- serum LDH (normal versus abnormal)

The system can define cohorts of patients in which to evaluate new therapeutic initiatives.

With regards to the importance of dose in the chemotherapy of NHL, again there is retrospective evidence that the dose intensity received might be another prognostic factor (although not necessarily independent from, for example, performance status or age). DeVita has used the method of Hryniuk and Bush to calculate the dose intensity of each drug and the average dose intensity of the combinations of drugs used in the treatment of diffuse aggressive lymphomas [29]. In order to do this it was necessary to construct a hypothetical nine-drug combination regimen using all drugs in full doses continually as a standard. The analysis showed a strong correlation between the nine-drug relative dose intensity and outcome ($r = 0.82$, $P < 0.0008$). However, there was no significant correlation between outcome and two or three drug-relative dose intensity. DeVita concluded that the success of third-generation regimens appears to be related to the use of more drugs, early exposure to non-cross-resistant agents and the high dose intensity. Furthermore, he suggested that further augmentation of dose may increase the fraction of patients cured.

The importance of dose intensity has also been demonstrated for the first-generation regimen cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP). A study by the SWOG showed that full-dose CHOP cured more patients (41%) than low-dose CHOP (12%) [13]. A retrospective study of 73 young patients with NHL treated with CHOP showed that the dose intensity of cyclophosphamide and doxorubicin in the first two treatment cycles was significantly correlated with event-free survival, but the dose intensity of these drugs in subsequent cycles and the dose intensity of other protocol drugs were not significantly associated with outcome, suggesting that the first three treatment cycles are most important.

In elderly patients, dose modification is common and may explain poorer treatment outcomes observed in some studies. Dixon *et al.* [31] observed that inferior outcomes for elderly patients in the SWOG trials may have resulted in part from less intensive chemotherapy. A subgroup of elderly patients who received full-dose chemotherapy has a higher complete response rate and higher overall survival than patients who received a low dose. In this context, haematopoietic growth factors are being actively investigated in the elderly, who tend to be more prone to myelosuppression.

However, data from 266 patients treated in phase II SWOG studies with m-BACOD, ProMACE-CytaBOM or MACOP-B showed that relative dose intensity was not significantly correlated with survival after adjusting for age and performance status [32]. A recent up-dated report on a very large randomised study conducted by the North American cooperative groups SWOG/ECOG, and presented by Fisher *et al.* at the American Society of Clinical Oncology meeting in 1992, showed no significant differences in outcome and survival on over 1000 patients treated with first generation CHOP (3 weekly) or new generation combinations, including weekly chemotherapies [33]. Some 1138 previously untreated patients with bulky stage II, stage III or stage IV NHL (intermediate or high grade) were randomised. Median follow-up was 31 months. At 4 years, the percentage of patients alive without disease for the different treatment protocols was: CHOP 36.4%; m-BACOD 34.4%; ProMACE-CytaBOM 45.1%; MACOP-B 38.8% (not statistically significant differences). On the other hand, fatal toxicities (without colony-stimulating factor therapy) showed some differences, perhaps reflecting the different intensities of therapy or a less balanced distribution of organ-related toxicities for the different drug combinations: 1% CHOP, 5% m-BACOD, 4% ProMACE-CytaBOM, 6% MACOP-B.

From the practical point of view, the main advantages of the weekly chemotherapy regimens like MACOP-B are the short overall duration of treatment (10–14 weeks); the fact that patients are seen once a week (so that action can be taken promptly to treat or prevent complications); and the idea that fast growing tumours should have no time to "re-grow" in between cycles. The main disadvantages are the higher toxicity (both haematological and non-haematological, like the mucositis often seen with the original MACOP-B protocol); the fact that an important drug like doxorubicin is usually not given at maximum cumulative doses (450–550 mg/m^2); and the realisation that when the original weekly protocols were tried in large multicentre studies, both CR rates and disease-free intervals were inferior to the original reported ones.

The use of recombinant human G-CSF has been shown to reduce myelosuppression and neutropenic fever, and to allow the administration of chemotherapy on schedule both for conventional CHOP-type chemotherapies [34] and for intensive weekly chemotherapies [35]. The Christie hospital group, in England, has recently described a randomised trial of filgrastim to preserve the dose-intensity of a new weekly regimen (VAPEC-B, which substitutes methotrexate for VP-16) in NHL [35]. Again, as for the multi-centre randomised phase III studies in small cell lung cancer, the prophylactic use of filgrastim reduced severe neutropenia and neutropenic fever by about 50%, and allowed the administration of chemotherapy on schedule without dose reduction in over 90% of patients. This resulted in slightly more thrombocytopenia and anaemia not complicated by clinical sequelae. As in a previous study with doxorubicin administered at high dose and dose rates [36], mucositis (and not severe neutropenia) became dose-limiting in some patients. Several European and American groups have gone a stage further and are now investigating the early use of high-dose therapy with G-CSF and circulating progenitor cells in subsets of patients at a high risk of relapse during first remission. One of these approaches involves the sequential use of high-dose cytotoxics (HDS therapies), but this is often done without anthracyclines (or giving low total doses of anthracyclines) which could prove counterproductive. In a more conservative, but equally interesting approach several groups are experimenting with CHOP given 2-weekly (rather than the conventional 3-weekly) with the help of rhG-CSF. Because of its rapid stimulation of neutrophil kinetics, rhG-CSF is ideally suited for this type of 2-weekly myelosuppressive therapy [37]. Steinke *et al.* [38] have recently reported a study in which 24 patients with high-grade NHL were treated with VIM/CHOP chemotherapy (alternating) at reduced intervals (down to 2-weekly): it was possible to apply chemotherapy in the scheduled reduced interval in more than 80% of the cycles without complications. The CR rate was 33% and the overall response rate 70%.

Thus, although the weight of clinical evidence, albeit retrospective, demonstrates that dose intensity is an important factor determining treatment outcome in lymphoma, and that excessive dose reduction or treatment delay is one of the most important reasons for failure to cure in NHL, we can accept that "less chemotherapy is worse", but we remain unsure as to whether "more chemotherapy" is necessarily better. What should one do in practice? Clearly this will depend on the clinical circumstances and on the personal experience and judgement of the clinician. Fernando Cabanillas [39], at the MD Anderson hospital, suggests two different clinical situations commonly encountered:

(1) A patient with Ann Arbor stage IVB, high serum LDH and beta-2-microglobulin, and bulky tumour mass will not do well with standard therapy such as CHOP. In some of these cases, the rate of relapse, even after apparent CR, is close to 70%. Intensive chemotherapies (with CSF and/or bone marrow +/− circulating progenitor cell support) should be investigated in this difficult group; (2) young patient with Ann Arbor stage III-A (or less) non-bulky disease, normal LDH and beta-2-microglobulin: prognosis is excellent with standard CHOP (or even CNOP, with mitoxantrone instead of doxorubicin).

Patients with refractory or recurrent lymphoma present several clinical problems and their therapy (which cannot yet be said to provide significant, more than 50%, and reproducible CR rates) should ideally remain linked to research protocols in an attempt to get valid and non-anecdotal answers. In this population of patients the prophylactic use of haematopoietic growth factors can be of particular help, considering that many of them have had extensive chemotherapy and, in some cases, also radiotherapy, leading to poor marrow function or decreased haematopoietic recovery. Moreover, bone marrow infiltration by lymphoma is not uncommon in these patients and they seldom tolerate conventional doses of cytotoxic drugs. On the other hand, these patients should be treated with maximum doses of drugs, in the hope that the apparently drug-resistant clones of tumour cells might become sensitive to higher doses of drugs (concept of "relative drug resistance"). This latter phenomenon, although infrequent, is probably seen more often in patients with Hodgkin's disease than NHL. Particular attention should also be paid to diffuse intermediate-grade lymphoma and immunoblastic lymphoma in the presence of a "divergent histology", or when diagnosis is based on a single extranodal site and no nodal tissue available for examination. A recent report suggests that 43% of these patients might suffer late relapses (after more than 24 months in complete remission), as opposed to the minimal risk of late relapse (less than 3%) commonly encountered in these conditions [40].

Histopathological features and the natural history of lymphomas in adults are not the same as lymphomas in childhood. Marrow and cerebrospinal fluid involvement in children are not infrequently seen in both T- and B-cell NHL. In the case of B-cell disease, heavy (more than 25%) infiltration of the bone marrow is usually classified as leukaemia and is characteristically associated with a high incidence of testicular and CNS involvement. Recombinant human colony-stimulating factors are now being investigated in children [41, 42] and are widely used in the paediatric clinics with very good responses. As David Nathan has recently put it: "children literally grow around their marrow as adulthood is achieved" [43]. The blood of the newborn, moreover, contains enough circulating stem cells to allow haematopoietic engraftment [44]. These factors may contribute to a better haematological tolerance of chemotherapy in children than in adults, and may be part of the reasons why children are more often cured even in the presence of disseminated disease. It is, therefore, no surprise that CSF are also successful in the management of children with lymphomas, both added to conventional protocols and in conjunction with intensive high-dose therapies with circulating progenitor cell support [45].

Combined radiotherapy–chemotherapy is commonly employed for stage I/II NHL and increasingly used also for Hodgkin's disease. One of the difficulties with this type of combined modality treatment is the myelosuppression which can lead to dose delays or dose reductions. Although no clinical studies have yet been fully published on the use of CSF in this setting, it is encouraging that several preliminary reports (including a Japanese randomised and double-blind controlled study) suggest that the administration of rhG-CSF to patients receiving radiotherapy has a definite and reproducible bone marrow protective effect [46]. However, the dose and timing of rhG-CSF administration in relation to the fractionation and timing of radiotherapy need to be defined better.

Finally, the optimal therapeutic approach for patients with advanced stage low-grade lymphomas (that represent the majority of patients with follicular small cleaved cell lymphomas) remains one of the most controversial areas in medical oncology. This is in spite of the fact that this disease is well known to respond to radiation therapy, single- and multiple-agent chemotherapy, combined modality treatment and, in some instances, immunotherapy. But the responses last for a median of 2 years only, and less than 10% of patients remain in remission for over 5 years [47]. Thus, the survival curves for patients with low-grade lymphomas are inevitably downwards due to continuous relapses, in contrast to many patients with high-grade NHL who achieve a complete and durable remission on front-line therapy. The use of high-dose therapy for low grade NHL is hotly debated. Why should one consider using it? According to some, to control symptoms in young patients; according to others, with a "curative" intent and because 4–6 years from diagnosis over 50% of patients will have transformed to high-grade NHL. However, in some classic Stanford studies, no difference in survival was found between single-agent chemotherapy (chlorambucil or cyclophosphamide) and cyclophosphamide, vincristine, prednisone (CVP) or CVP combined with radiotherapy [48]. Several intensification studies have been reported, but results are either negative, or data are still too preliminary to draw definite conclusions. The advent of recombinant human CSF is allowing the exploration by several cancer centres of high-dose cyclophosphamide and total body irradiation, or high-dose therapy and ABMT (or circulating haematopoietic progenitor cells) in selected groups of patients with low-grade NHL.

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