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Debate on the conservative and aggressive treatment options for the optimal management of indolent non-Hodgkin's lymphoma

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Indolent non-Hodgkin's lymphoma (NHL) is currently considered to be an incurable disease, with a median survival of 6–8 years. In the absence of a cure, the variety of therapeutic options available for patients with indolent NHL range from 'watchful waiting' to high-dose therapy (HDT) with autologous stem-cell transplantation (ASCT). There is no current consensus on standard treatment. Conventional chemotherapy is clearly not curative, and many clinicians prefer to delay chemotherapy until the patient develops overt symptoms that require treatment. On the one hand, long-term studies indicate that 'watchful waiting' has no effect on overall survival. On the other hand, aggressive treatment strategies, such as HDT with ASCT, may increase disease-free survival in some patients, particularly when used early in the treatment algorithm, but are also associated with potential toxicity. Thus the selection of therapy for each patient involves balancing the benefit of the treatment with any side effects and detriment to quality of life. The development of innovative therapies for indolent NHL, such as monoclonal antibodies with or without chemotherapy, requires a reassessment of the treatment choices. Good clinical responses and time to progression have so far been achieved in clinical trials of rituximab and other agents including radiolabelled antibodies, but in view of the long median survival of patients with indolent NHL, it will be some years before it can be conclusively demonstrated whether such treatments have an effect on the natural history of the disease or produce a cure. This issue raises an important question: outside the setting of a clinical trial, should patients be treated aggressively with therapies that do not yet have proven curative ability? This article considers the evidence and relative merits for the conservative approach to indolent NHL, where patients are treated according to symptoms in order to maintain a normal quality of life wherever possible, and for the aggressive approach, where the lymphoma is targeted soon after the diagnosis. [© 2002 Lippincott Williams & Wilkins.]

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Introduction

The treatment of patients with indolent non-Hodgkin's lymphoma (NHL) represents a significant challenge to the clinician. While many patients with aggressive NHL can be cured with anthracycline-based regimens such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), no current treatment regimen has demonstrated improved survival in patients with indolent disease. Although the majority of patients initially respond well to a variety of therapies, relapse is almost universal, and patients may receive several different therapies, usually with a progressively shorter duration of remission, before they eventually die of their lymphoma. Despite the ultimately poor prognosis of indolent NHL, patients have a median survival of almost 8 years, and many patients live for considerably longer than 10 years. The effect of treatment on patients' quality of life, therefore, is very important.

The monoclonal antibody rituximab has recently emerged as an effective therapy for indolent NHL, and in combination with chemotherapy (immunochemotherapy) has achieved very high response rates and durable remissions.[1,2] Rituximab acts via multiple mechanisms that are distinct from those of chemotherapy, and it is not yet known whether, in contrast to standard chemotherapy, immunochemotherapy will have an effect on overall or disease-free survival. Other novel agents such as radiolabelled antibodies are also being evaluated in indolent NHL, and the availability of these agents, as well as autologous stem-cell transplantation (ASCT), has considerably expanded the range of treatment options. Due to the natural history of the disease, long periods of follow-up (10 years or more) are required before survival differences can be expected from randomized trials. In the meantime, the role of

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newer therapies for indolent NHL remains unclear. This review assesses the available evidence for the application of various therapy options, both conservative and aggressive, in the treatment of patients with indolent NHL.

Standard therapies for indolent NHL – 'watchful waiting' and chemotherapy

The concept of 'watchful waiting' in indolent NHL is based on the premise that, since treatment does not increase survival, no treatment should be given until the patient shows symptoms that require it. Adopting this strategy has been demonstrated to delay the use of chemotherapy by 2–3 years, and studies of 'watchful waiting' compared with initial chemotherapy have demonstrated no difference in survival (Table 1).[3–6] During the early stages of disease, therefore, avoiding the use of toxic therapies can help maintain patients' quality of life. Against this factor, however, it is important to consider the psychological implications for the patient associated with waiting for their disease to progress rather than proactively undertaking treatment.

If a patient with asymptomatic disease is given treatment, rather than 'watchful waiting', it is clearly important that the therapy option chosen should have the lowest toxicity possible. When chemotherapy is used, therefore, a mild regimen such as chlorambucil or cyclophosphamide, vinblastine and prednisone (CVP) has generally been the first option. More recently, the human/mouse chimeric monoclonal antibody rituximab has emerged as an effective treatment for indolent NHL, with low toxicity. Rituximab is licensed for the treatment of relapsed and chemoresistant low-grade and follicular NHL and is now being evaluated as a first-line therapy.[7] An overall response rate of 54% was obtained using rituximab as a first-line therapy in 39 patients with follicular NHL or small lymphocytic lymphoma, while Colombat *et al.*[8,9] demonstrated an overall response rate of 73% (60% complete response) with rituximab as the first-line treatment in 50 asymptomatic patients with follicular NHL. These data indicate that rituximab is effective as a first-line treatment, and, since it is well tolerated, it could be an alternative to 'watchful waiting'. It remains to be determined, however, whether the use of rituximab at an early stage results in benefits such as delaying the need for chemotherapy or prolonging disease-free survival. Furthermore, lymphoma cells that survive prior exposure to rituximab may develop resistance mechanisms which in turn could decrease this agent's efficacy on repeat use.

The sequence of treatment options

Indolent NHL follows a chronic relapsing and remitting course, and many patients will eventually receive most available treatment options. Since none have yet been shown to influence survival, it could be argued that the order in which the treatments are given is irrelevant. However, the first treatment option chosen will be received by the largest number of patients, as some patients will not receive later therapies, either because they have stayed in remission or because they have died of their lymphoma or of other causes. The order in which therapies are used thus has significant implications in terms of both cost and toxicity. Given three agents with the arbitrary unit costs 1, 5 and 10, if the least expensive agent is used first, fewer patients will ultimately receive the most expensive therapy, and overall treatment costs for a given number of patients will be less (Figure 1). Similarly, utilizing the least toxic agent first will mean that fewer patients receive the more toxic therapies, resulting in an overall lowering in toxicity and consequently an improvement in quality of life. Such a model, of course, assumes that the various treatments given do not impact on overall survival, regardless of order in which they are used.

Table 1. Results of a 'watch and wait' policy in asymptomatic or low-bulk, advanced, indolent NHL

Reference	Group	*n*	Median time to treatment (months)[a]	Overall survival (%)	
				5 years	10 years
Horning and Rosenberg[3]	Stanford	83	36	82	73
Young *et al.*[4]	NCI	44	34	75	NR
O'Brien *et al.*[5]	Edinburgh/Birmingham	59	33	56	NR
Brice *et al.*[6]	GELA	66	24	78	NR

GELA, Groupe d'Etude des Lymphomes de l'Adulte; NR, not reported.
[a]Excludes local radiotherapy.

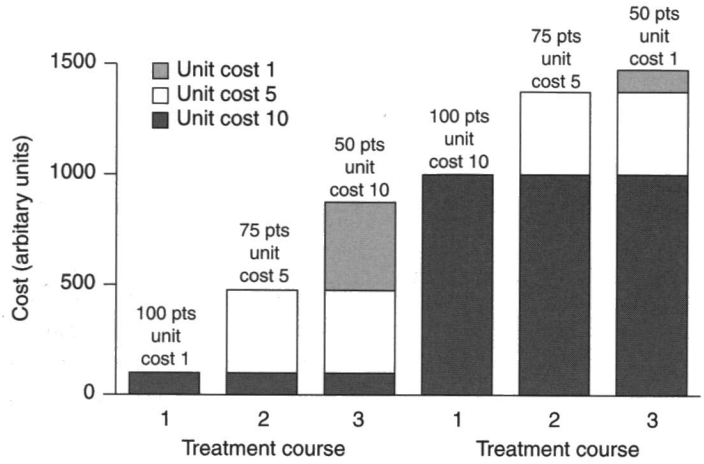

Figure 1. Cost impact of the sequence in which treatments are used. The costs differ depending on the order in which the three agents, costing 1, 5 and 10 arbitrary units, are used. pts, patients.

Should more aggressive treatments be used at an early stage?

It is clear that the standard chemotherapy regimens that have been in use for several decades do not improve survival, but the impact of newer therapies, such as monoclonal antibodies and other biological agents, remains to be determined. Clinical trials are underway, but since patients with indolent NHL have a very long median survival, even if untreated, studies require a long follow-up period (10 years or more) if they are to demonstrate a significant benefit for a new agent. The question remains, therefore, as to whether there is sufficient justification for the use of aggressive, new therapies, with curative intent, at an early stage of treatment outside the setting of a clinical trial.

One argument for the earlier use of new treatments is that, by treating with conventional chemotherapy and/or 'watchful waiting', one may actually reduce the curative potential of later treatments if the disease progresses and becomes more resistant. Bulky disease is a known adverse prognostic factor for response to rituximab, and therefore 'watchful waiting' may result in less responsive disease.[7,10] It has long been known that the duration of response to chemotherapy decreases with each consecutive treatment, suggesting that treatment with chemotherapy may result in disease more resistant to later, more aggressive treatments (Figure 2).[11] The earlier use of aggressive regimens, such as the addition of interferon-α to CHOP-like chemotherapy, has yielded some promising results in follicular lymphoma, resulting in longer progression-free and overall survival than CHOP-like chemotherapy alone.[12,13] However, other studies have failed to show a benefit for interferon-α in follicular NHL.[14,15]

Autologous stem-cell transplantation

High-dose chemotherapy with ASCT is a potentially curative treatment for patients with relapsed aggressive NHL although its use in indolent NHL is still being evaluated. What is clear from several studies, however, is that the most significant adverse prognostic factor for disease-free and overall survival following ASCT for indolent NHL is the number of prior chemotherapy regimens. In a study of 60 patients with poor-prognosis follicular lymphoma, the only significant prognostic factor was the number of previous chemotherapies, and similar findings were obtained by Bierman *et al.*[16,17] in a retrospective study of 100 patients undergoing autologous peripheral blood or bone marrow transplantation. These findings argue that, if ASCT is to be used, it would be best employed at an early stage of treatment. The toxicity of ASCT, however, precludes its use in patients over the age of 65–70 years.

Combination of monoclonal antibodies with chemotherapy

As indicated earlier, the monoclonal antibody rituximab is effective in indolent NHL and has an excellent safety profile. Rituximab acts via different mechanisms to conventional chemotherapy and may

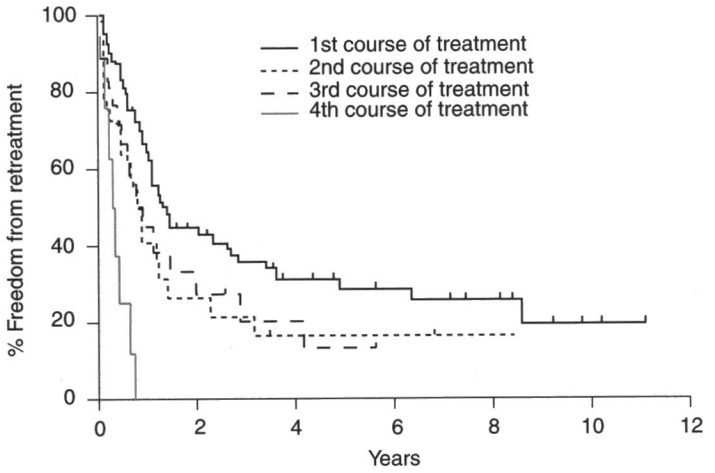

Figure 2. Median duration of remission decreases with sequential standard chemotherapy, suggesting increasing chemoresistance to therapy. Reproduced with permission from Gallagher et al.[11]

act synergistically with some chemotherapeutic agents.[18–21] Combining rituximab with chemotherapy, therefore, offers the potential to increase efficacy without significant added toxicity over chemotherapy alone. A phase II study of rituximab plus CHOP chemotherapy in patients with indolent NHL has yielded an overall response rate of 100% (63% complete response rate) in the 35 patients who completed treatment.[1] The median time to progression in these patients has not yet been reached with more than 5 years' median follow-up.[2] This appears somewhat longer than the time to progression previously achieved with CHOP alone for indolent NHL.[22] Randomized studies are required to confirm this, and these are currently underway. The combination of rituximab plus fludarabine has also been evaluated in indolent NHL, with an overall response rate of 90% (80% complete response rate), minimal non-hematologic toxicity and acceptable hematologic toxicity.[23]

As we await the results of randomized studies to determine conclusively whether new treatments such as immunochemotherapy can improve disease-free and overall survival in indolent NHL, evidence of improved efficacy can be provided by surrogate markers. The *bcl-2* oncogene is overexpressed in more than 85% of cases of follicular NHL due to a t(14;18) chromosomal translocation. The resulting gene rearrangement can be detected by the highly sensitive polymerase chain reaction (PCR) and provides a valuable marker of minimal residual disease in blood and/or marrow. In the stem-cell transplantation setting, the persistence of the *bcl-2* rearrangement after transplant correlates with significantly worse disease-free survival.[24] The combination of rituximab plus CHOP chemotherapy resulted in six of seven patients with detectable *bcl-2* rearrangement at baseline converting to *bcl-2* negativity.[1] Previous studies have demonstrated that chemotherapy alone rarely results in clearance of detectable *bcl-2*-positive cells.[25] These findings further suggest that immunochemotherapy may represent an improvement on conventional chemotherapy for indolent NHL.

Monoclonal antibodies in the ASCT setting

Relapse following ASCT for indolent NHL is caused by malignant cell contamination of the stem-cell graft or by residual malignant cells in the patient not killed by the high-dose chemotherapy. *In vivo* purging with rituximab involves administration of the antibody before and/or during stem-cell mobilization to eliminate malignant cells from the circulation before the stem cells are harvested. Several studies have now demonstrated that rituximab *in vivo* purging is effective, in that PCR-detectable *bcl-2*-positive cells can be removed from the stem-cell harvest and the patient.[26–28] Also, the addition of rituximab is well tolerated, with no adverse effect on engraftment, hematologic recovery or long-term outcome. The administration of radiolabeled antibodies in combination with ASCT has also been evaluated in indolent NHL, with ^{131}I-tositumomab used as 'targeted radiotherapy' in place of total body irradiation.[29] Initial results suggest that the use of radiolabeled antibodies could lead to longer disease-free and overall survival compared with historical controls given total

body irradiation. The long-term toxicity of using radiolabeled mouse antibodies in this setting is not known.

Conclusion

The optimal treatment strategy for indolent NHL remains unclear; however, with the emergence of novel biological therapies, particularly rituximab, it is possible to achieve increased efficacy without significantly increasing toxicity. The clinical trials required to demonstrate that strategies such as immunochemotherapy may improve survival will require very long follow-up, and therefore the question remains as to whether these therapies should be used outside the clinical trial setting in the hope of achieving a cure for individual patients. Patients with the poorest prognosis may be candidates for more aggressive and experimental therapies, including ASCT. In the meantime, the data that are available suggest that immunochemotherapy may offer an improvement over conventional treatment. At the moment, it remains the clinician's decision as to which patients should be given standard, conservative treatments, such as 'watchful waiting', and which patients might benefit from more aggressive therapies.

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