Follicular lymphoma: Grounds for optimism

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Summary

The fact that follicular lymphoma is characterized by a specific immune phenotype and a nonrandom chromosomal translocation which may be detected at the molecular level makes it possible to design novel therapeutic strategies for curative therapy. Molecular markers may be used to test hypotheses. Some current causes for optimism are reviewed.

Key words: follicular lymphomas, t(14;18)

Background

Follicular lymphoma is widely perceived as an indolent illness, on the basis of its relatively long (for a malignant disease) 'natural history' [1] and the fact that progression may be slow enough for no intervention to be necessary for several years [2]. This, coupled with the finding that immediate moderately intensive therapy for patients with nontroublesome advanced disease has not been shown to yield an overall survival advantage over expectant management [3], may have allowed both complacency and negativism to influence the management of patients with the disease over the past twenty years. Thus, today as in 1986 [4], the average patient may be expected to live about 10 years, having had 3 episodes of lymphadenopathy 'responsive' to relatively innocuous therapy, after which time 'resistance' may have occurred or transformation supervened. It is therefore good that there are glimmerings of hope that treatments other than alkylating agents given alone or in combination may also be effective, and 'allowing' consideration of novel therapeutic strategies which might result either in cure or better palliation. Proving that a promising novel treatment is better than another demands, cost aside, either that it improves quality of life or that it prolongs it. So far, the latter goal has been elusive because of the repeated responsiveness of follicular lymphoma and its relatively long clinical course with conventional therapy. To date, only one manoeuvre, namely, combination therapy with chemotherapy and interferon [5], has been shown in randomized trial to prolong life, and other reasonably similar studies have failed to confirm this, despite also showing prolongation of complete remission [6].

It may be that the presence or absence of cells bearing the nonrandom t(14;18) translocation at the molecular level will become, if not a reliable surrogate marker of cure, a possible indication for continuing or stopping therapy. There are obvious caveats to this hypothesis [7-9]. It is at least supported by a Boston study finding that high-dose consolidation chemoradiotherapy supported by 'PCR-negative' autologous bone marrow transplantation yields significantly longer remission than when t(14;18)-bearing cells are reinfused [10]. It seems reasonable to proceed on the assumption that the achievement of a t(14;18)-negative state is a sensible goal.

Grounds for optimism?

Interferon 'maintenance'

The report that treatment with an adriamycin-containing chemotherapy combination given with interferon resulted in longer remissions and survival than the same chemotherapy alone can only be ignored after great consideration [5]. Longer follow up may strengthen the observation. However, in one study (Rohatiner et al., personal communication) patients entering complete remission with chemotherapy remained 'PCR positive' from the t(14;18) even after continuation interferon. Thus, in this case, cure seems an unlikely outcome of the treatment: this does not, of course, negate its possible value.

High-dose chemotherapy and autologous bone marrow transplantation

Comparison with historical controls suggests strongly that this treatment prolongs second remission [11]. In this group of patients, despite in vitro antibody therapy of the infused marrow, almost none of the patients received t(14;18)-negative stem-cell harvest [12]. Interestingly, the overall freedom-from-recurrence pattern was the same as that achieved in the study from Boston alluded to above [10]. The side effects of the therapy are substantial, making it inappropriate for the elderly, with a worrying incidence of myelodysplasia being reported [11, 13, 14]. It must be emphasized, however, that the contribution of prior therapy cannot be excluded. The use of peripheral
blood progenitor cells to support the procedure, with various positive selection and depletion procedures, may increase the applicability and efficacy of the therapy [15–17]. Concern about the potential morbidity and mortality of this treatment has inevitably resulted in its evaluation later rather than earlier in the disease. Newly published data about its use in first remission may be interpreted positively or negatively [18]. Phase III trials are in progress in Europe to compare it with CHOP in second remission. More data are obviously required, but for some patients this therapy might be appropriate, particularly if complemented by immunotherapy (see below).

**Purine analogs**

There is a large body of evidence to suggest that the purine analogs, particularly fludarabine [19–23] and 2-chlorodeoxyadenosine [24–26] induce remission, usually partial in patients with recurrent and refractory follicular lymphoma. The overall response rate in previously untreated patients has been reported to be 65% with 37% entering complete remission [27]. There is no substantial data about freedom from progression. However, since the overall response rate is rather lower than might be expected with an alkylating agent alone, even if the complete remission rate is rather higher, it seems unlikely that given alone this treatment will be curative. It is highly likely to have a role at least in palliation, in the treatment algorithm, particularly when an oral formulation is available.

Potentially more exciting are reports of its use in combination with mitoxantrone and dexamethasone. High complete remission rates have been reported [28, 29]. More important, the peripheral blood has been found to be free of t(14;18)-bearing cells. Clinical follow-up will determine the significance of this, but the finding allows speculation about developing a curative strategy without myeloablative therapy.

**Antibody therapy**

Phase II/III trials of the chimeric anti-CD20 antibody (IDEC) in patients with recurrent and refractory follicular lymphoma show a response rate of about 50% but also, as above with chemotherapy, the achievement of a t(14;18)-free state in the peripheral blood [30]. These latter results must be viewed with particular caution of course, since the treatment by definition depletes the peripheral blood of B lymphocytes. The major toxicity of the therapy occurs with the first injection of antibody, and is usually limited to chills and shaking. Hospital admission has been a rarity. Hence this therapy has considerable potential, regardless of its ability to cure. It might be used as the treatment of first choice with a view to avoiding altogether (probably unlikely) or postponing chemotherapy. This in itself would be a major advance. On the other hand, it might be used with chemotherapy, or afterwards, in the context of 'minimal residual disease'.

**Antibody delivered irradiation**

Iodine-131 has been conjugated to the murine anti-CD20 antibody B-1 (Coulter) in both low and high doses and in the selected cases in which appropriate 'pretreatment' dosimetry has been satisfactory, yielding very high response rates in patients with recurrent and refractory follicular lymphoma [31, 32]. The overall management is somewhat complex at present, demanding admission to hospital while the patient is 'hot', as well as hematopoietic stem-cell support for the high-dose therapy. No data have yet been published about the effect of the therapy on the t(14;18)-bearing cell population. Freedom-from-recurrence data are hard to interpret in the light of extensive prior therapy. However, both high- and low-dose therapies have substantial promise for the future, either alone or, in the case of the high-dose as an alternative to total body irradiation, as myeloablative therapy or again as an adjunct to chemotherapy.

**Idiotype vaccination**

It has now been clearly demonstrated that vaccination with idiotype and a nonspecific immune stimulant of patients in remission of follicular lymphoma results in humoral immune response about half the time [33, 34]. Further, those patients in whom these responses were achieved had a better freedom-from-recurrence pattern than the rest. This is most exciting, but there are drawbacks. First, the immunogenicity of the vaccine needs to be increased. This may be possible with cytokines [35]. Second, it is impracticable outside the confines of a relatively small clinical trial, because of the procedure for preparing the vaccine. It may be possible to circumvent this by the use of a DNA vaccine [36, 37] for which phase I trials are in progress. These problems notwithstanding, it seems possible that it will shortly be possible to test on a large scale the efficacy of active immunotherapy after cytoreductive treatment. This is timely, since the means are now available to achieve pretty 'complete' remissions with intensive chemotherapy: the minimal-residual-disease setting in which it could be postulated that immunotherapy might be most likely to work.

**Improvements in costimulation and antigen presentation**

Further from introduction into conventional therapy are alternative biological approaches. These may be critical if any form of immunotherapy is to be successful, but various strategies could be explored [38, 39].

**Antisense therapy**

It is now possible to synthesize antisense oligonucleotides for the t(14;18) translocation. These are now the subject of phase I trials [40, 41]. That such treatment will be relevant alone seems unlikely, but it might form part of an overall plan, either to treat patients in combination or
in sequence with other therapy, or as \textit{ex vitro} manipulation of bone marrow to support high-dose therapy.

**Conclusion**

Many novel ways of treating patients with follicular lymphoma are now almost available for testing in large clinical trials. There is much promise in them, at the very least for expanding palliative capacity, possibly with less toxicity. For the optimist, some of the data suggest that cure may be round the corner.

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**References**

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