Follicular lymphoma: side-lined drug excites new interest

Janet Fricker

A study showing that follicular lymphoma patients benefit from adding interferon to standard chemotherapy has opened up new avenues for research.

A meta-analysis has shown that using interferon in addition to chemotherapy leads to longer periods of remission and longer survival in patients with follicular lymphoma. The study published in the April 1 issue of the *Journal of Clinical Oncology* (vol 23, pp 1-9) analysed data on 1,922 patients with follicular lymphoma, treated in the context of 10 phase III trials that had produced conflicting results.

Follicular lymphoma represents the second most common histological sub-type of non-Hodgkin's lymphoma (NHL), accounting for 35% of lymphomas in North America and 22% worldwide. The median age at diagnosis is 59 years, with the incidence being slightly higher in men than in women. "The median survival is 9 or 10 years, virtually irrespective of the type of treatment," said Ama Rohatiner, Professor of Haemato-Oncology at St Bartholomew's Hospital in London and the principal investigator of the study. "With conventional therapy, response rates are about 80%, but the illness virtually always comes back."

Treatments vary depending on age and stage at presentation, from a 'watch and wait' strategy in the initial stages to multi-agent chemotherapy. Treatment options in current use include fludarabine-based regimens, treatments containing anti-CD20 (rituximab/MabThera), radioimmunotherapy, and high-dose treatment supported by autologous haematopoietic progenitor cells.

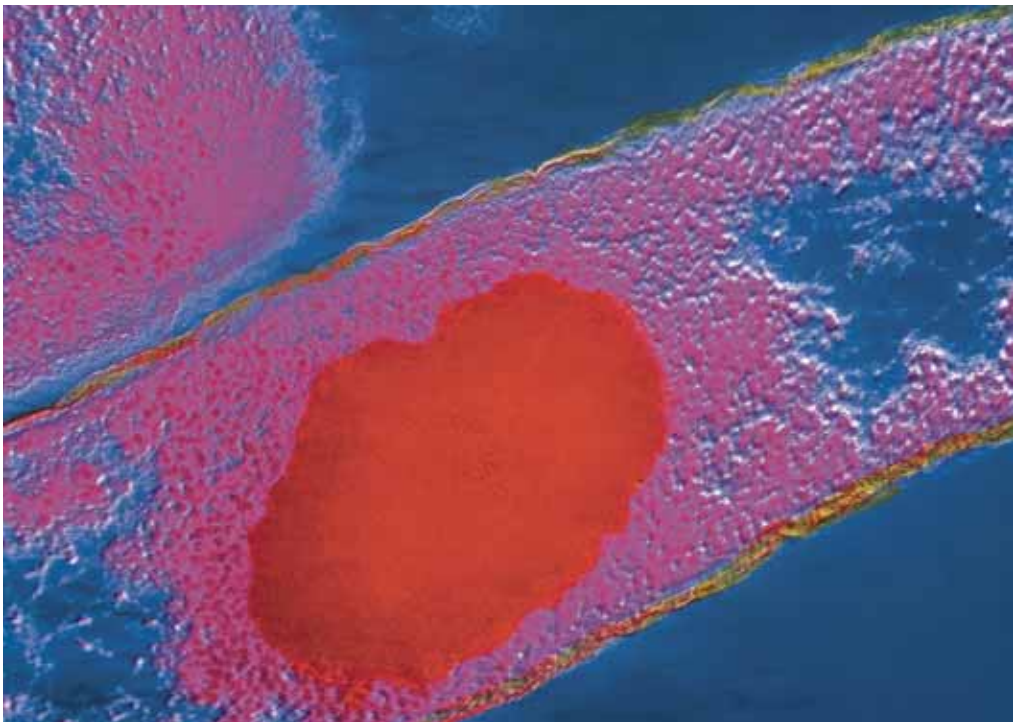
Yesterday's drug?

"Since the inception of the study, the use of interferon α-2 [IFN α-2] for follicular lymphoma has been largely superseded by these newer treatments" said Rohatiner. Patients today are rarely treated with IFN α-2 since its clinical toxicity is not negligible. It needs to be given by subcutaneous injection, and causes flu-like symptoms and fatigue. "But while the newer drugs cause fewer side effects, show higher response rates and longer durations of response, with the exception of high-dose therapy, they have yet to show an improvement in survival," she added.

The rationale for performing the meta-analysis came from a series of 10 randomised studies, published between 1991 and 2001, evaluating the use of IFN α-2 given in conjunction with chemotherapy to newly diagnosed patients. The problem was that considerable heterogeneity between studies led to conflicting results, which made it difficult to reach a consensus. Discrepancies in the results occurred even when only studies of similar design were considered.

- In some studies IFN α-2 was given concurrently with chemotherapy; in others it was used as 'maintenance' therapy, whilst in others it was used throughout.
- Chemotherapy regimens varied in intensity, from relatively low doses of alkylating agent (chlorambucil or cyclophosphamide) to doxorubicin or mitoxantrone-containing regimens. Doses and schedules of IFN α-2 also differed.
- Additional variability occurred because some studies allowed the use of radiotherapy to sites of bulky disease at presentation, or to residual disease.

The meta-analysis was therefore undertaken to clarify the effect of interferon on response, duration of response and survival. Investigators from the original studies were approached and asked to provide updated patient information, with only patients diagnosed with follicular lymphoma being included in the final



CNRI / SCIENCE PHOTO LIBRARY

E.coli synthesising human interferon

analysis. Chemotherapy regimens were categorised by the intensity of chemotherapy, with studies utilising relatively 'less intensive' chemotherapy being defined as those using chlorambucil, cyclophosphamide, or cyclophosphamide/vincristine/prednisolone (CVP) as initial therapy, whilst regimens using anthracycline or mitoxantrone-based combinations were considered 'more intensive'.

Overall, the study found that IFN α-2, when given in addition to conventional chemotherapy as part of initial therapy in newly diagnosed patients with follicular lymphoma, prolongs remission duration and survival, but does not result in any improvement in response rate. Exploring these differences in greater detail, the investigators found that interferon increased survival in patients in whom the drug was given in conjunction with relatively intensive chemotherapy, at a dose of at least 36 million units/month.

The authors acknowledge that, with the development of alternative treatments, it is difficult to know "how best to incorporate this information into the algorithm of therapy". Michele Ghielmini, Associate Professor of Oncology at the Oncology Institute of Southern Switzerland, agrees. "If rituximab didn't exist, this paper would have been enough to convince me to use interferon, but now it's probably a bit late to be helpful," he said.

But the study is valuable in that it points the way to future research. "We know that rituximab and chemotherapy is better than chemotherapy alone, and from this study that interferon and chemotherapy is better than chemotherapy alone, so perhaps we should now be investigating whether the combination of chemotherapy, interferon and retuximab in follicular lymphoma would be even better still," he said.

Interferon increased survival in patients when given together with fairly intensive chemotherapy