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Editorial

Towards a Cure in Indolent Lymphoproliferative Diseases?

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CLASSIFICATION OF lymphoproliferative diseases further improved with the publication of the Revised European–American Lymphoma (REAL) classification [1], which encompasses previously described diseases and newly recognised or individualised lymphoma entities. This classification was based on morphological immunological and genetic characteristics of the different entities, and differs from the Working Formulation for Clinical Usage [2] that classified lymphomas according to conventional morphology and outcome. Chronic lymphomas/leukaemias include chronic lymphocytic leukaemia (CLL), prolymphocytic leukaemia (PLL), small lymphocytic/lymphoplasmocytoid lymphomas (SL/LPL), small lymphocytic lymphoma, immunocytoma, and large-cell rich immunocytoma (LCRI)), large granular lymphocytic leukaemia, and hairy cell leukaemia. Nodal or extranodal lymphomas with indolent presentation include follicle centre lymphoma (FCL), epidermotropic T-cell lymphoma (ETCL: mycosis fungoides and Sezary syndrome), marginal zone B-cell lymphoma (MZL: MALT lymphomas, monocytoid B-cell lymphoma, and splenic lymphoma with/without villous lymphocytes), and mantle cell lymphoma (MCL). Characteristics of these two groups of lymphoproliferative diseases are the indolent and apparently benign onset of the disease, the difficulty in obtaining complete remission (CR) with current therapies, except in localised cases, the disease transformation into large cell lymphomas (Richter's syndrome), and the constant annual death rate of 5–10% a year without hope of cure [3, 4].

In this issue, two reviews present current therapeutic possibilities in lymphoma (pp. 2141–2145) and CLL (pp. 2146–2154) patients. The common feature of these two reviews is the appearance of therapeutic strategies that may lead to an increase in the cure rate in the near future. While cure is the goal of first line treatment in large cell lymphoma patients, and can be achieved in at least 50% of patients younger than 65 years [7], indolent lymphomas and CLL are still considered to be incurable diseases. In this setting, recommendations appear in the literature for delaying treatment in these patients until disease progression and a need for treatment because of the appearance of disease-related symptoms (poor performance status, large tumour mass, cytopenia, high lactic dehydrogenase or β2-microglobulin levels . . .) [8, 9]. An initial delay in treating patients did not appear to be detrimental for patients in early studies: median treatment-free survival was 3–4 years in small cell FCL patients, 5 to 6 years in SL/LPL patients, but only 1–2 years in small and large cell FCL patients. However, very few, if any, trials compared an intent to treat delayed treatment versus standard treatment with overall survival as the main endpoint.

In FCL, the "watch and wait" modality and intensive chemotherapy (ProMACE–CytaBOM) followed by total lymphoid irradiation were randomly compared in a study initiated by the National Cancer Institute, U.S.A. [10]. A recent update of this trial demonstrates a higher rate of complete remissions in patients treated with intensive chemotherapy and radiotherapy, but no differences in survival after a median follow-up of 8 years [11]. The inclusion rate in this trial was very low and it is impossible to detect a small difference between the two treatments. In a French randomised study, FCL patients with low tumour burden were treated with chlorambucil or interferon or were not initially treated [12]: no differences in progression-free survival or overall survival was demonstrated with a median follow-up of more than 5 years. Differences between these two trials are important: in the NCI trial, all FCL patients were included and those randomised in the "watch and wait" arm received local radiotherapy for large nodal mass(es); those randomised in the chemotherapy arm received a more intensive therapy compared to chlorambucil for the French trial; only FCL patients with low tumour burden were included in the French trial. Nevertheless, the conclusions of these two trials are identical: there are no adverse effects of delaying the treatment; there is no increase in patients with histological transformation of the tumour in the delayed treatment group; the response rate is unaltered if treatment is delayed; and the death rate and low cure rate are similar to previous studies.

In CLL, randomised trials have shown that delaying treatment until progression occurs has no detrimental effect on low risk patients' survival [13]. In one trial, chlorambucil treatment was associated with more adverse events than delaying treatment [9]. In these trials, low risk patients were defined as Binet stage A or Ral stage 0.

In both diseases, untreated patients have to be assessed regularly because progression nearly always occurs. Progression

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is defined by increasing volume of lymph nodes, appearance of large tumoral mass(es), appearance of poor performance status, increase in lymphocyte counts with less than a 1 year doubling time, appearance of cytopenia, increase in lactic dehydrogenase (LDH) or β2-microglobulin levels, and appearance of infectious or haemorrhagic complications. Histological transformation may be observed at the time of progression, particularly in FCL patients, and it is associated with resistance to treatment and poor outcome. A standard chemotherapy regimen needs to be established.

Delaying treatment is considered the best "therapeutic" strategy for low tumour burden patients with indolent presentation, and this was justifiable when these diseases were incurable. This option is always acceptable for elderly patients who have a high probability of having other debilitating diseases over the following 10 years after diagnosis. It should no longer be considered the standard and recommended therapeutic option for younger patients. 5 or 10 year survival is not satisfactory for young patients and alternative therapeutic options should be proposed and developed. For years, standard therapeutic options were limited to either single agent chemotherapy (chlorambucil or cyclophosphamide) given continuously or a few days a month, or combination chemotherapy, that is, CVP (cyclophosphamide, vincristine, and prednisone), or CHOP (CVP plus doxorubicin). Numerous trials have shown that there is no advantage for one of these regimens over the others [14–20] and, in comparison, initial no treatment was associated with a better quality of life without a detrimental effect on patient survival.

However, new therapeutic modalities have appeared in recent years for patients with a more aggressive disease at diagnosis or for those that progressed after standard treatment or no treatment at all. They have modified disease response to treatment, progression-free survival, and survival for patients with the most aggressive forms at diagnosis. In FCL patients, whose need for initial treatment was unquestioned because of bulky tumour(s), poor performance status, B symptoms, or cytopenia(s), addition of interferon to initial chemotherapy or as consolidation therapy has been shown to be associated with longer progression-free survival in all comparative trials [21] and with longer survival in the GELF trial [22]. While interferon therapy may be associated with benefit in other indolent lymphomas [23], no such benefit has been observed in CLL patients [24].

Fludarabine was introduced some years ago for the treatment of refractory CLL and indolent lymphoma patients [25, 26], and was associated with high response rates and long remission duration. While fludarabine efficacy in newly diagnosed patients is even more important [27, 28], its exact role as first line treatment alone or in combination [29] remains to be defined. The place of other purine analogues, such as 2-chlorodeoxyadenosine [30] or deoxycoformycin [31], is also yet to be defined. Definitive conclusions will not be known until the large on-going comparative trials are closed and analysed [32].

High dose therapy (HDT) with autologous or allogeneic stem cell support has only been used in this setting for a short period of time and longer follow-up is necessary to draw definitive conclusions. However, early results in relapsing FCL patients have demonstrated that longer disease-free survival may be obtained with higher dose therapy, possibly associated with total body irradiation (TBI) [33–35]. Similar results have been obtained for FCL patients whose tumour transformed into a more aggressive lymphoma [36]. Interpretation of these results are complicated by the fact that they come from non-randomised studies with some patient selection. However, in one study, disease-free survival was longer than control matched patients [35], and in another, disease-free survival after HDT was longer than progression-free survival before high dose therapy in most of the patients [36]. HDT with stem cell support (SCT) has also been proposed for CLL patients [37–40]. While allogeneic transplant is limited in CLL patients because most patients are elderly, it may have potential for the youngest patients with aggressive forms at diagnosis and good response to initial therapy. Autologous purged or non-purged peripheral blood stem cell transplants have been used in recent years because of the very good response obtained with fludarabine. The number of patients treated with such a procedure is relatively low and no definitive conclusions may be drawn. However, in this small group of patients, procedure-related complications were low, mainly infectious complications related to neutropenia and chronic immune deficiency, and continuing complete remission has been observed. This therapeutic strategy will certainly develop, but it must currently be considered experimental and reserved for carefully well designed studies. Nevertheless, it is a promising hope for these "incurable" patients.

The conclusion of all these studies is the emerging idea that indolent lymphomas and CLL may be curable diseases and that those patients should not be considered beyond treatment. Only preliminary results have so far been presented, often in very selected patients, so they may not reflect the situation for most "standard" patients, but these results are sufficiently important to indicate that our current strategies are not definitive. For the future, these new modalities have to be developed in carefully designed randomised trials to demonstrate their benefit in terms of survival. Survival is the only valid endpoint for these indolent diseases and response to treatment or duration of response can only be considered to be encouraging data. Indolent lymphoma and CLL should not be considered as "favourable", since these diseases are fatal, but new therapeutic modalities may at least prolong patient survival. These patients must be included in prospective trials, which is the only way to improve their outcome, as recently shown in a retrospective analysis of a population-based registry [41].

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