Potential long-term toxicities should influence the choice of therapy for indolent non-Hodgkin’s lymphoma

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The optimal management of indolent non-Hodgkin’s lymphoma (NHL) remains controversial. In 2006, treatment strategies for indolent NHL include observation, chemotherapy, rituximab, radioimmunotherapy, autologous and allogeneic stem cell transplantation, and external beam radiation therapy. With the possible exception of autologous stem cell transplantation, these options are not curative. However, several recent studies suggest improved survival of patients with follicular lymphoma treated in the modern era compared with historical controls. This suggests that the choice of both initial and subsequent therapies may affect the natural history of the disease. A recent analysis from the United States National Lymphocare Study, a registry of follicular lymphoma, showed that widely diverse regimens are utilized in the treatment of the disease in the United States, and that significant differences in approach are observed between regions of the country and between academic centers and private practice settings.

Historically, the therapeutic approach to indolent NHL consisted of alkylating agent-based chemotherapy. The role of anthracyclines was, and remains, controversial. Over the past 15 years, there has been increasing enthusiasm in some centers for the use of purine analog-based chemotherapy, often in combination with either alkylating agents or anthracyclines. Indeed, some of the highest response rates in the treatment of follicular lymphoma have been observed following fludarabine-based combination chemotherapy. Zinzani and colleagues compared fludarabine plus mitoxantrone with CHOP chemotherapy, in a prospective randomized clinical trial, and concluded that fludarabine plus mitoxantrone was superior to CHOP in terms of complete response rates (71% vs. 51%). However, progression-free and overall survival were not significantly different between these regimens when rituximab was utilized. The MD Anderson Cancer Center has incorporated fludarabine-based combination chemotherapy with rituximab as a standard approach to the upfront therapy of indolent lymphoma over the past several years. Improvements in 5-year failure-free survival, with a possible plateau on the failure-free survival curve, compared to that historical controls after adjusting for prognostic factors suggest that more active front line therapies (incorporating fludarabine) may have affected the natural history of the disease. However, the aforementioned observations of improved overall survival for patients with follicular lymphoma treated over the past several years in other institutions not utilizing fludarabine suggests that it is the incorporation of antibody-based treatments, including non-myeloablative radioimmunotherapy, rather than the specific regimen of chemotherapy, which has led to the overall survival benefit. With this improved survival, patients with indolent lymphoma have more time to develop secondary effects of chemotherapy and radiation therapy. Historically, myelodysplastic syndrome (MDS) and secondary acute myelogenous leukemia (AML) have been recognized as significant complications of alkylating agent-based chemotherapy for both indolent NHL and Hodgkin’s lymphoma. Topoisomerase inhibitors also clearly contribute to the risk of MDS/AML. Autologous stem cell transplantation (ASCT), which prolongs disease-free survival in a subset of patients with indolent NHL, represents the lymphoma treatment modality with the highest risk of causing MDS/AML. Secondary MDS/AML has an exceedingly poor prognosis in this group of patients, and is the leading cause of non-disease-related death in survivors of ASCT for lymphoma.

There is a positive relationship between the cumulative dose of alkylating agents or topoisomerase II inhibitors and the risk of developing secondary MDS/AML. In general, the peak incidence of MDS/AML occurs 4-6 years after the initiation of cytotoxic therapy, although latency periods as short as 12 months (particularly for patients treated with topoisomerase II inhibitors) and as long as 15-20 years (in the setting of radiation exposure) have been reported. The majority of patients with MDS/AML after therapy for NHL present with complex karyotypes. Deletions of chromosomes 5 and 7 are most common, and several candidate genes that influence hematopoietic growth and differentiation are located in the 5q segment. Aberrant expression of growth factors on this chromosome may promote leukemic transformation, and the entire 5q gene segment appears to be intrinsically unstable, and particularly vulnerable to damage from cytotoxic therapy in the setting of radiation or high dose chemotherapy.

In this issue of Haematologica, Tam and colleagues retrospectively report a high incidence of treatment-related MDS in a cohort of patients with indolent NHL treated with fludarabine combination chemotherapy in either the upfront or relapsed setting. Among 137 patients treated with fludarabine combination regimens, including fludarabine plus mitoxantrone with rituximab and fludarabine-cyclophosphamide with rituximab and mitoxantrone plus rituximab, 16 patients (12%) developed MDS/AML, with a median time to diagnosis of 45 months (range 5-147 months).

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ses of MDS/AML. These reports are summarized in Table 1.

However, this report is in keeping with other recent
reports implicating purine analog chemotherapy, particu-
larly when given in combination with other agents, as
a potential contributor to the development of MDS/AML.
These reports are summarized in Table 1. The MD
Anderson investigators have reported the inci-
dence of MDS following fludarabine plus mitoxantrone
chemotherapy with dexamethasone. Of 202 patients
treated, eight developed MDS/AML between 1 and 5
years after therapy, including four who received no
additional chemotherapy. The CALGB reported a
lower incidence of MDS in a group of patients with
chronic lymphocytic leukemia treated with chlorambucil
and fludarabine, but warned that the use of alkylator-
pu- rine analog combination therapy appeared to
increase the expected risk of MDS. Other case reports
have suggested that MDS/AML following fludarabine
therapy may occur earlier than expected after alkylat-
ing-agent based chemotherapy.

In the series reported by Tam et al., of the ten
patients who developed MDS/AML following fludara-
bine combination therapy, two were also treated with
autologous bone marrow transplantation. Despite dif-
f erences in methods used to identify cases and to esti-
mate the cumulative incidence over time, it is now
well-known that up to 10% of patients with NHL
treated with autologous bone marrow or ASCT may
develop secondary MDS/MDL within 10 years of pri-
mary therapy. The separate contributions of pretrans-
plantation and transplantation-related therapy were
assessed in a case-control study of 56 patients with
MDS/AML after ASCT for lymphoma, and 168
matched controls. This study clearly demonstrated
that the intensity of pretransplant therapy contributed
to the risk of developing MDS in this setting. In a
cohort of patients treated at St. Bartholomew’s
Hospital, 230 patients with NHL treated with
ASCT, 27 subsequently developed MDS. In multivari-
ate analysis, prior fludarabine therapy was a signifi-
cant risk factor for the development of MDS. The
Cleveland Clinic recently published their experience
concerning MDS following ASCT for lymphoma. Fludarabine
was administered as a single agent or in
combination to 42 patients with NHL before ASCT.
Fludarabine exposure remained a significant risk factor
for the development of subsequent MDS in multivari-
ate analysis, and also made stem cell collections more
difficult.

Two patients in the series reported by Tam et al. also
received axial radiation therapy, and one patient
radioimmunotherapy, prior to the development of
MDS. An increased incidence of MDS and AML has
been clearly linked to previous exposure to radiation.
In one series of patients treated with low dose total
body irradiation and chemotherapy for NHL, the 15-
year estimated cumulative incidence of MDS was
17%. In patients undergoing ASCT, a higher inci-
dence of non-relapse related mortality, including
MDS/AML, has been observed in patients treated with
external beam radiation therapy. The true incidence
of MDS after non-myeloablative radioimmuno-
therapy with either 131I-tositumomab or Y90-
ibritumomab tiuxetan remains to be defined. In a registry
study, MDS/AML was reported in 35 (3.5%) of 995 patients
(annualized incidence, 1.6%/year) treated with 131I-
tositumomab, with a short median follow-up. The
incidence of MDS after Y90-ibritumomab tiuxetan
appears to be similar. However, long-term follow-up
of larger cohorts of patients is clearly required to de-
finitively determine the incidence of this fatal complica-
tion in the modern treatment era of indolent lymph-
oma, and the degree to which radioimmuno-
therapy contributes to this risk.

Therapeutic strategies for treatment-related
MDS/AML are limited. The outcome of MDS/AML in
Tam’s series was very poor: 80% of patients have
died so far. This is in keeping with the outcome of
MDS/AML following ASCT for lymphoma, in which
even allogeneic stem cell transplantation does not lead
to a cure in the vast majority of cases. Therefore,
efforts need to be made to avoid this complication

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whenever possible. In Hodgkin’s lymphoma, a number of ongoing multi-institutional randomized trials are investigating different ways to reduce treatment, including the omission of radiation therapy, minimization of toxic chemotherapy, and the adaptation of response-based therapy. The introduction of novel biological treatment options for NHL, including monoclonal antibody therapy, proteasome inhibitors, and vaccines may allow future minimization of such toxic therapy in the treatment of indolent NHL.

What can be concluded about the use of fludarabine combinations in the treatment of indolent NHL? Despite significant clinical activity, they do not appear to be curative, and they clearly appear to at least contribute to the risk of MDS/AML. Prolonged follow-up of randomized trials incorporating fludarabine-based combinations is required for a definitive quantification of the risk of this complication. Clearly, if ASCT is to be considered an eventual therapeutic option for a patient with indolent NHL, avoiding prolonged exposure to fludarabine-based combinations seems warranted. The report by Tam et al. in this issue of Haematologica would support this notion. There are many possible upfront therapies for indolent lymphoma. The choice of which upfront therapy to use must consider not only response rates, and time to progression, but also the impact on future therapies, including transplantation, and risk of secondary malignancies. Failure-free survival at 3 or even 5 years is an inadequate end-point for providing physicians and patients true information about overall risks and benefits of a therapeutic regimen. It is imperative that current clinical trials in de novo indolent NHL, including the United States Intergroup study comparing CHOP + rituximab to CHOP + 1st-tositumomab, follow these patients for late effects. Our recent success of improving short-term outcome for these patients with novel agents is accompanied by a responsibility to ensure that we do not compromise their future survival due to late toxic effects of treatment.

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**References**