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 allogeneic 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.[1,2] 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.[3]

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.[4] 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.[5] 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,[6] rather than the specific regimen of chemotherapy, which has led to the overall survival benefit.[1] 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,[7] 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.[8] 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.[9]

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.[10] Among 137 patients treated with fludarabine combination regimens, including fludarabine plus mitoxantrone with rituximab and fludarabine-cyclophosphamide with rit-

uximab, ten patients (7%) developed MDS/AML a median of 40 months following fludarabine combination therapy. The cumulative incidence of MDS at 40 months was estimated to be 6%, but anticipated to increase further by Kaplan-Meier analysis. The rate of MDS was higher (15%) in patients with follicular lymphoma than in those with other indolent histologies, and in patients who had been exposed to increasing numbers of prior therapies. This is the major limitation regarding the data presented: it is impossible to determine the exact contribution of fludarabine combination therapy since all but one patient received other agents that have been demonstrated to cause MDS/AML.

However, this report is in keeping with other recent reports implicating purine analog chemotherapy, particularly 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 incidence 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.[11] 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-purine analog combination therapy appeared to increase the expected risk of MDS.[12] Other case reports have suggested that MDS/AML following fludarabine therapy may occur earlier than expected after alkylating-agent based chemotherapy.[13,14]

In the series reported by Tam *et al.*,[10] of the ten patients who developed MDS/AML following fludarabine combination therapy, two were also treated with autologous bone marrow transplantation. Despite differences in methods used to identify cases and to estimate 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 primary therapy.[15] The separate contributions of pretransplantation 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.[16] 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, of 230 patients with NHL treated with ASCT, 27 subsequently developed MDS. In multivariate analysis, prior fludarabine therapy was a significant risk factor for the development of MDS.[17] The Cleveland Clinic recently published their experience concerning MDS following ASCT for lymphoma.[18] 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 multivariate analysis, and also made stem cell collections more difficult.

Table 1. Risk of MDS/AML following fludarabine combination chemotherapy.

Author	*Disease*	*Incidence*	*Median follow-up (months)*	*Therapy*
McLaughlin[11]	NHL	8/202 (4%)	42 mos	FM+Dex
Morrison[12]	CLL	6/544(1%)	50 mos	F + Chlorambucil
Tam[10]*	NHL	10/137 (7%)	40 mos	FMR or FCR

*FCR: fludarabine/cyclophosphamide/rituximab, FM(R)=fludarabine/mitoxantrone/rituximab. *The study by Tam et al. included some patients who were treated with autologous stem cell transplantation prior to developing MDS/AML.*

Two patients in the series reported by Tam *et al.*[10] 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%.[19] In patients undergoing ASCT, a higher incidence of non-relapse related mortality, including MDS/AML, has been observed in patients treated with external beam radiation therapy.[20] The true incidence of MDS after non-myeloablative radioimmunotherapy with either I^{131}-tositumomab or Y^{90}-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 I^{131}-tositumomab, with a short median follow-up.[21] The incidence of MDS after Y^{90}-ibritumomab tiuxetan appears to be similar. However, long-term follow-up of larger cohorts of patients is clearly required to definitively determine the incidence of this fatal complication in the modern treatment era of indolent lymphoma, and the degree to which radioimmunotherapy contributes to this risk.

Therapeutic strategies for treatment-related MDS/AML are limited. The outcome of MDS/AML in Tam's series[10] 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.[22] Therefore, efforts need to be made to avoid this complication

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, proteosome 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 + I^{131}-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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