Secondary malignancies after therapy of indolent non-Hodgkin's lymphoma

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Indolent non-Hodgkin's lymphoma remains incurable with standard therapeutic modalities. For three decades between 1970 and 2000, despite the introduction of new classes of agents, new modalities such as autologous stem cell transplantation, and improved supportive care, there was no improvement in the overall survival of patients with indolent lymphoma.[1] Over the past decade, however, information from several datasets suggests that there has been a dramatic, significant improvement in overall survival of patients with follicular lymphoma.[2,3] This improvement is likely due to the routine incorporation of rituximab and other therapeutic monoclonal antibodies in the treatment paradigm for these diseases. Indeed, randomized studies demonstrate improved overall survival when rituximab is combined with chemotherapy, compared to chemotherapy alone as upfront therapy for follicular lymphoma.[4]

With this improved survival, patients with indolent lymphoma have more time to develop secondary effects of chemotherapy and radiation therapy. The risk of solid tumors after treatment for lymphoma has been best established in Hodgkin's lymphoma. However, as therapies for indolent lymphomas have improved, it is expected that risks and risk factors for the development of solid tumors in patients with such lymphomas may be similar to those of patients with Hodgkin's lymphoma. In the modern Hodgkin's lymphoma therapeutic era (ABVD treatment era), lung and breast cancer, often appearing 15 or more years after completion of lymphoma therapy, have emerged as the most significant subtypes of second malignancy, accounting for the majority of cases.[5,6]

Radiation therapy is the most significant risk factor for developing solid tumors after lymphoma, with the majority of second cancers arising either within or at the edges of radiation fields. Large studies have suggested that cancers of the esophagus, stomach, rectum, breast, bladder and thyroid may all be secondary to radiation, with clear evidence of increased risk with increasing dose of radiation.[7-9] The contribution of chemotherapy alone to the development of solid tumors in patients with Hodgkin's and non-Hodgkin's lymphoma has historically been less clear. In a cohort of patients with Hodgkin's lymphoma studied by the British Lymphoma Investigation Group, the relative risks of developing lung cancer after radiation therapy alone or chemotherapy alone were both significantly increased at 2.9 and 3.3, respectively.[10]

Reports on the relationship between age at diagnosis and treatment of lymphoma and risk of second malignancy are conflicting. One consistent finding, however, is the increased risk of breast cancer among females treated for Hodgkin's lymphoma at a young age. This is largely secondary to mantle fields of radiation, and may not be relevant to patients with indolent non-Hodgkin's lymphoma. The cumulative incidence of second malignancy in children treated for Hodgkin's lymphoma approaches 26% at 20 years, emphasizing the prolonged period of risk, and the significance of this problem.[11]

Historically, myelodysplastic syndrome (MDS) and secondary acute myelogenous leukemia (AML) have been recognized as significant complications of alkylating agent-based and topoisomerase inhibitor-based chemotherapy for indolent non-Hodgkin's lymphoma. Autologous stem cell transplantation, which prolongs disease-free survival in a subset of patients with indolent non-Hodgkin's lymphoma, represents the lymphoma treatment modality associated with the highest risk of developing MDS/AML. Secondary MDS/AML has an exceedingly poor prognosis in this group of patients, and represents the leading cause of non-disease-related death in survivors of autologous stem cell transplantation for lymphoma.[12]

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 (in the setting of 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 non-Hodgkin's lymphoma present with complex karyotypes. Deletions of chromosomes 5 and 7 are most common.

The true incidence of MDS/AML and other secondary malignancies after treatment for indolent lymphoma, outside of the setting of autologous transplantation, is largely unknown. Historical series have suggested that the incidence of secondary malignancies is almost double the expected incidence over a 10-year follow-up period and patients treated with total body irradiation have an even higher risk.[13-15]

In this issue of the journal, Sacchi and colleagues present long-term follow-up information on a cohort of 563 patients with indolent non-Hodgkin's lymphoma enrolled in Italian clinical trials between 1988 and 2003.[16] In this cohort, 39 patients (almost 7%) developed a second cancer, including 12 with MDS/AML. As expected, the median time to diagnosis of MDS/AML was 25 months from the diagnosis of non-Hodgkin's lymphoma. The most common solid tumors reported were lung, gastrointestinal and breast cancers.

This study demonstrated that the overall risk of sec-

ondary malignancy in this cohort of patients with indolent non-Hodgkin's lymphoma was significantly increased compared to the risk of malignancy in the general Italian. A multivariate analysis demonstrated that increased patient's age, male gender, and a history of fludarabine-based treatment were predictive of developing a secondary malignancy.

The analysis by Sacchi *et al.* does, however, have several limitations. There is no cytogenetic information available to confirm the secondary nature of MDS/AML. In fact, there is no confirmatory pathology information available for any of the secondary tumors, as expected for a registry analysis. Only 29% of the patients were initially treated with rituximab-containing regimens, thus limiting the applicability of the findings to the current era. Moreover, many of the initial chemotherapy regimens utilized (including BACOP, ProMECE-CytaBOM, and high dose chlorambucil with epidoxorubicin) are moderately to highly aggressive alkylating-agent heavy regimens that are not commonly utilized in the modern era for indolent lymphoma. The data in the paper are biased toward these regimens, as the longest follow-up is for patients treated with chlorambucil. Finally, almost half of the patients had received at least a second line of chemotherapy treatment for their lymphoma; details on these treatments are lacking. It is unknown, for example, whether any of these patients had been treated with autologous stem cell transplantation.

Despite these limitations, it is interesting that fludarabine therapy emerged as a significant risk factor for the development of secondary malignancies, particularly solid tumors. Other studies have suggested an increased incidence of MDS/AML when fludarabine is incorporated into the treatment paradigm for indolent lymphoma. Based on a retrospective analysis, Tam and colleagues reported a high incidence of treatment-related MDS in a cohort of patients with indolent non-Hodgkin's lymphoma treated with fludarabine combination chemotherapy in either the upfront or relapsed setting.[17] Among 137 patients treated with fludarabine combination regimens, ten patients (7%) developed MDS/AML a median of 40 months following the fludarabine combination therapy. The cumulative incidence of MDS at 40 months was estimated to be 6%. Investigators from the MD Anderson Center reported the incidence of MDS following chemotherapy with fludarabine, mitoxantrone and dexamethasone. Of 202 patients treated, eight developed MDS/AML between 1 and 5 years after therapy, including four who received no additional chemotherapy.[18] Clearly, purine analog therapy is emerging as a major risk factor for MDS/AML in the setting of indolent lymphoma, with risks similar to those reported for alkylating agents.

Understanding the baseline risk of secondary malignancies, particularly MDS/AML, in patients with indolent lymphoma is critical in order to be able to evaluate the safety of new agents. Ever since the early trials of radioimmunotherapy, there has been concern that MDS/AML could be a late complication of this therapeutic modality. This concern has limited the development of these agents, and is frequently cited as a reason for withholding radioimmunotherapy from patients.[19]

Czuczman and colleagues recently reviewed a database including 746 patients treated with ibritumomab tiuxetan radioimmunotherapy.[20] At a median of 4.4 years of follow-up, there were 19 cases of secondary AML or MDS with a crude incidence rate of 2.5%. Interestingly, comparing patients who developed secondary MDS/AML with those who did not, follicular histology and prior treatment with a purine analog were the only significant differences in risk factors. The association with purine analog treatment remained significant even in multivariate analysis; fludarabine was the purine analog in all cases. Increased age, prior radiation and alkylating agents did not seem to be overly represented in the patients who developed AML or MDS after ibritumomab tiuxetan. Similar risks have been reported with iodine-131 tositumomab, although the purine analog treatment status of those patients did not appear to increase the risk of MDS/AML.[21]

Importantly, the use of upfront radioimmunotherapy has not been associated with MDS or AML,[22] except when combined with chemotherapy.[23] One other important finding in the study by Sacchi and colleagues was that the cumulative incidence of secondary cancers continued to increase over the period of follow-up without evidence of a plateau. As previously mentioned, this phenomenon has been recognized in the setting of breast cancer after treatment of Hodgkin's lymphoma, in which increased risk continues to be present for up to 30 years after radiation therapy. Longer follow-up of this and other non-Hodgkin's lymphoma cohorts will be important to define the period of risk, which will have implications for the follow-up of these and other patients treated for indolent non-Hodgkin's lymphoma.

Decreasing treatment intensity, and avoiding known causative agents such as radiation therapy, autologous stem cell transplantation, and now perhaps purine analog therapy, appear to be the key ways of preventing the development of secondary MDS/AML.

Few studies have suggested ways to decrease the risk of solid tumors after therapy for lymphoma. Several case-control studies have evaluated tobacco use as an additional risk factor for developing secondary neoplasms after therapy for lymphoma.[9,24] In one study, in which the smoking history was known for 90% of the population considered, patients who smoked more than 10 pack-years after Hodgkin's lymphoma had a 6-fold higher risk of lung cancer compared to those with a less than 1 pack-year history of smoking.[25] Moreover, a multiplicative effect between smoking and lymphoma therapy exposure has been demonstrated: patients who received both radiation therapy and alky-

lating agents were at a 7-fold increased risk of lung cancer; this risk increased to 49-fold among patients with a greater than 10-year history of tobacco use.[9] Sacchi and colleagues did not report smoking status in their cohort of patients, but it is likely that smoking may have contributed to the risk of lung cancer.

Second malignancies have clearly evolved to be important causes of morbidity and mortality in patients with indolent lymphomas. As survival times increase, and the cohort of patients treated with modalities such as purine analogs, aggressive autologous transplantation and novel radioimmunotherapy grows, it can be expected that the incidence of second cancers will increase significantly. Perhaps most concerning is the lack of an apparent plateau in the incidence curve, even 20-30 years after diagnosis of lymphoma. For this reason, it is critical that patients in prolonged remission remain under care of medical and radiation oncologists attuned to these risks, and undergo at least annual evaluation (history and physical examinations), with appropriate screening tests for second cancers. In the future, emphasis must continue to be given to minimizing toxic therapy to prevent this devastating cost of cure.[26] Finally, it is important to realize that the risk of MDS/AML associated with radioimmunotherapy may not be substantially different from the risk in patients treated with standard chemotherapy, including both alkylating agents and purine analogs.

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