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Therapy-related myeloid neoplasms in lymphoma survivors: Reducing risks

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ABSTRACT

Treatment for Hodgkin (HL) and non-Hodgkin's lymphoma (NHL) has changed dramatically in the last fifty years. While there are increasing numbers of long-term survivors, there has been increasing recognition of the long-term toxicities of treatments, particularly therapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/AML). The survival for t-MDS/AML is extremely poor. Multiple heterogeneous retrospective studies have reported risk factors for the development of t-MDS/AML. Chemotherapy and radiation therapy have been most closely examined as possible t-MDS/AML risk factors. In this paper, we will review the risks of t-MDS/AML for HL and NHL patients as reported in the literature and assess for any changes over time. In HL patients, the incidence of t-MDS/AML has decreased with a reduction in alkylating agents. In indolent NHL patients, we anticipate decreased incidence of t-MDS/AML as targeted therapies begin to replace cytotoxic chemotherapy.

1. Introduction

The treatment spectrum for both Hodgkin (HL) and non-Hodgkin lymphomas (NHL) has continued to evolve over the last several decades and has led to significant improvements in disease and patient outcomes. Cytotoxic chemotherapies such as alkylating agents and anthracyclines have been the backbone of lymphoma therapy for the last few decades. While the immediate toxicity profiles for the different classes of anti-lymphoma therapies are generally well-described, long term effects and risks of delayed life-threatening toxicities including treatment-related malignancies have been more difficult to characterize fully. Therapy-related myelodysplastic syndrome (t-MDS) and acute myeloid leukemia (t-AML) are recognized as devastating complications associated with many standard cytotoxic therapies. Therapy-related MDS/AML generally occurs within ten years of treatment. Multiple factors have previously been associated with increased risk including age, exposure to leukemogenic agents and radiation therapy. Much of the available data is from the review of large databases and registries where there are multiple confounding variables including differences in treatment regimens and patient populations. As more information emerges, there are unifying assessments as well as continued unanswered questions. In this paper, we will review the available literature for both HL and NHL as well as the impact of hematopoietic stem cell transplant. While newer agents are rapidly being developed and altering treatment paradigms in lymphoma, there is limited data on their relationship to t-MDS/AML or impact on the underlying stem-cell compartment.

Any review of future risk, often characterized as the incidence of a condition, should begin with a short discussion of methodologies. When discussing incidence, it is essential to recognize a variety of reporting measures are reflected in the literature. Crude incidence (number of patients diagnosed with t-MDS/AML divided by total number of patients) will generally underestimate the true

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incidence as new cases are diagnosed with additional follow-up. Statistical methods have been used to define an actuarial estimate of the t-MDS/AML incidence; however, actuarial estimates can overestimate the true incidence if they ignore competing risks. The Kaplan-Meier method has been used to determine an actuarial estimate of the risk of t-MDS/AML but ignores competing risks (e.g., the cause of death from heart disease). Estimation by Kaplan-Meier poses a risk of overestimation as time goes by and the number of censored patients continues to increase, a problem that can be avoided using the cumulative incidence estimate [1]. Cumulative incidence has been used by many studies to estimate the percentage of patients who will be diagnosed with t-MDS/AML in a specified time interval in the presence of competing risks. For example, a 10-year cumulative incidence of 7% implies that if 100 patients are treated today and we wait ten years, it is estimated that 7 of the patients will have been diagnosed with t-MDS/AML before death from another cause. Other studies report relative risk (RR) which measures the rate of an event among different cohorts of patients. Excess absolute risk (EAR) is the difference in risk between exposed and control populations. For example, if the risk of AML in the general population is 1% and the risk of AML in the study group is 6%, the EAR is 5%.

2. Secondary myeloid malignancies In Hl

Hodgkin lymphoma is the most common cancer diagnosed in teenagers ages 15 to 19 [2]. Disease-free, and overall survival rates have improved significantly in the last few decades [3]. Improvements in both chemotherapy and radiation therapy have translated into a significant clinical benefit with 5-year survival rates estimated at 86% [2]. Given the young age at diagnosis and expected survival, assessment, enumeration and mitigation of long-term complications have been critical in the HL population. It has been recognized that mortality related to treatment can persist for at least 25 years, and in some cases, exceeded the risk of death from HL [4,5]. Recognition of long-term toxicities has been a driving force behind many of the recent clinical trials seeking to de-escalate chemotherapy and radiation therapy while maintaining efficacy.

The risk of t-MDS/AML in HL has been recognized for several decades [6]. Alkylating agents have been strongly implicated in t-MDS/AML. MOPP (Mechlorethamine, vincristine, prednisone, and procarbazine), which utilizes two alkylating agents, was one of the early chemotherapy regimens leading to long term survival in HL patients. In a case-control study of 1939 patients treated in the Netherlands between 1966 and 1986, the cumulative dose of mechlorethamine emerged as the most critical factor in determining leukemia risk [7]. As compared to patients treated with RT alone, patients treated with 6 or fewer cycles of combinations including mechlorethamine and procarbazine had an 8-fold increased risk of developing leukemia; patients who received more than six cycles of same chemotherapy had a greater than 40-fold increase in the risk of leukemia.

Similarly, Stanford reported on 754 newly diagnosed HL patients treated between 1974 and 2003 with 5 years of follow-up [8]. Both the radiation and chemotherapy regimens evolved over time. After 1992, all patients (n = 256) received minimal alkylator therapy on the Stanford V regimen (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, and prednisone) followed by involved field RT (IFRT). Twenty-four patients (3.2%) developed t-MDS/AML, 15 after first-line chemotherapy and nine after salvage therapy. Twenty of the 24 patients with t-MDS/AML received chemotherapy with MOPP or PAVe (procarbazine, mechlorethamine, vinblastine); none of the patients treated with Stanford V developed t-MDS/AML after first-line treatment. Median age at t-MDS/AML diagnosis was 41 years with median latency time from primary HL treatment until t-MDS/AML diagnosis of 4.6 years. The median overall survival was dismal at 0.7 years. Both the Stanford and the Netherlands datasets provided support for limiting the cumulative dose of alkylating agents to reduce the incidence of t-MDS/AML.

The current treatment strategies for HL continue to rely on cytotoxic chemotherapy agents. In the US, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) remains the most commonly used regimen for newly diagnosed HL patients [9]. From selected data, ABVD appears to have a lower risk of t-MDS/AML as compared to alkylator agent-heavy regimens [7,10]. An Italian retrospective analysis reported on 1032 consecutive HL patients treated with RT or chemotherapy or both between 1965 and 1978 [11]. Chemotherapy regimens varied over time, but were mainly MOPP, ABVD or mechlorethamine, doxorubicin, bleomycin, vincristine, prednisone (MABOP). Overall, ten patients were diagnosed with t-AML. There were no cases of AML in patients receiving RT alone or in patients receiving ABVD. The risk of t-AML appeared to be highest for patients treated with salvage chemotherapy (5.2%) as compared to those initially treated with combination therapy (1.2%). In particular, patients receiving MOPP + RT had a 6.5% actuarial risk of AML; patients receiving ABVD + RT had 0% actuarial risk of t-AML.

Etoposide, a topoisomerase-2 inhibitor with well-described leukemogenic toxicity, is part of the BEACOPP (Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) regimen established by the German Hodgkin Study Group (GHSG) for advanced-stage HL patients [12,13]. $BEACOPP_{escalated}$ utilized higher doses of cyclophosphamide, etoposide and doxorubicin than $BEACOPP_{baseline}$ in attempt to improve efficacy [13]. In the GHSG HD9 study, 1201 advanced-stage HL patients were randomly assigned to eight cycles of COPP/ABVD, $BEACOPP_{baseline}$ or $BEACOPP_{escalated}$, At 10-year follow-up of the HD9 study, there were one, seven and 14 cases of t-MDS/AML in the COPP/ABVD (n = 261), $BEACOPP_{baseline}$ (n = 469) and $BEACOPP_{escalated}$ arms (n = 466), respectively [14]. The estimated 10-year cumulative incidence of t-MDS/AML was 0.4% for the COPP/ABVD arm as compared to 2.2% for the $BEACOPP_{baseline}$ and 3.2% for $BEACOPP_{escalated}$ arms (log rank test: p = 0.030). Based on the improved freedom from treatment failure (FFTF) and overall survival (OS), $BEACOPP_{escalated}$ was selected as the backbone for future GHSG studies. There has been concern that increased use of etoposide would translate into increased t-MDS/AML risk. GHSG retrospectively analyzed 11952 newly-diagnosed HL patients enrolled on 11 GHSG trials between 1993 and 2009 [15]. At a median follow-up of 72 months, the overall t-AML/MDS rate was 0.9% (106 patients). Among the analyzed patients, 51% received BEACOPP. To better understand the correlation between chemotherapy intensity and risk of t-MDS/AML, the patients were divided into three groups: no BEACOPP (49%), less than 4 cycles of $BEACOPP_{escalated}$ (23%) and 4 or more cycles of $BEACOPP_{escalated}$ (28%). Of the 106 patients with t-MDS/AML, 23% received no BEACOPP, 19% received less than 4 cycles, and 58% received greater than 4 cycles of

$BEACOPP_{escalated}$. The cumulative incidence rate (CIR) of t-MDS/AML for the respective 3 groups was 0.3%, 0.7% and 1.7% ($p < 0.0001$). The median time from HL treatment to t-MDS/AML diagnosis was 31 months; however, more than 20% of the t-MDS/AML patients were diagnosed 5–10 years after treatment. The median patient age of t-MDS/AML patients was higher than the whole group, 43 vs. 34 years. In multivariate analysis, in addition to age and number of BEACOPP cycles, extended field radiation therapy (EFRT) was also associated with t-MDS/AML. The median OS for the afflicted patients was a sobering 7.2 months.

The administration of RT continues to evolve in HL. While chemotherapy alone has been studied in select early-stage patients, RT remains a primary treatment modality for most early-stage patients. Over the last few decades, the radiation doses and fields have evolved in an attempt to minimize long term toxicity, primarily secondary malignancies including connective tissue, thyroid, lung and breast neoplasms, and cardiac toxicity [16,17]. In the GHSG report, EF-RT was noted to be associated with t-MDS/AML in multivariate analysis [15]. In an Italian cohort study of 1659 HL patients followed for a median of 10 years, the overall 15-year actuarial risk of acute leukemia was 4.2% [18]. Similar to other studies, the risk was lowest with RT alone (0.3%) and highest for the group receiving RT + MOPP + lomustine (15.6%). The overall duration of chemotherapy was a risk factor for leukemia but also the extent of RT, principally patients receiving extended RT involving the abdomen and pelvis. Of note, there were no cases of acute leukemia in patients treated with ABVD alone. While it is hypothesized that modern RT practices are associated with lower rates of t-MDS/AML, a recent meta-analysis challenges this view [19]. In 2397 early-stage patients, there was no difference in incidence rates of t-MDS/AML between extended vs. involved-field RT at a median follow-up of 10.8 years. Similarly, in 2962 early-stage patients, there was no difference in incidence rates of t-MDS/AML between RT at higher doses vs. RT at 20 Gy at a median follow-up of 7.4 years. The meta-analysis did not address risk with RT involving the abdomen and pelvis as described in the Italian study. In the current era, the risk of t-MDS/AML with RT alone appears to be quite low. The changes in RT occurred over the same time interval as many of the chemotherapy changes including reduction in alkylating agents which confound detection of discreet change.

Overall, it appears that the incidence of t-MDS/AML is declining among HL survivors. In a study of more than 35,000 individuals who survived for at least one year following treatment for HL, 217 individuals were diagnosed with AML (10.8 expected; unadjusted EAR) = 6.2; 95% confidence interval (CI) 5.4 to 7.1) [20]. The EAR for AML was highest in the first ten years after HL diagnosis but persisted. The EAR declined after 1984 which was presumed to be due to changes in chemotherapy. It was again confirmed by another report of 3905 HL patients in the Netherlands treated between 1965 and 2000 [16]. Median age of patients at the start of treatment was 28.6 years; median follow-up was 19.1 years with a minimum of 5 years. The sub-distribution hazard ratio was statistically decreased in the period from 1965 to 1976 as compared to 1989–2000. Again, the change in the hazard ratio was attributed to a reduction in alkylating agents. A small, yet significant risk of t-MDS/AML persists after HL treatment with high disease-related mortality and merits continued investigation.

3. New therapies in Hodgkin lymphoma

While cytotoxic chemotherapy remains the primary therapy for HL, several new drugs have entered the treatment realm. Brentuximab vedotin, an antibody-drug conjugate, was initially approved by the Federal Drug Administration (FDA) for relapsed/refractory HL following autologous stem cell transplant [21]. More recently, brentuximab vedotin was approved by the FDA in combination with the AVD backbone for first-line treatment of stage III/IV classical HL [22]. The regimen had a higher rate of neutropenia and required prophylactic granulocyte colony-stimulating factor (G-CSF). Long term toxicity has not yet been reported and may be difficult to assess given the already low rate of t-MDS/AML with ABVD. Nivolumab and pembrolizumab, PD-1/PD-L1 blocking antibodies, have also been approved for relapsed/refractory HL [23,24]. Clinical trials are evaluating checkpoint inhibitors earlier in the disease course and in combination with other therapies such as brentuximab vedotin. While we anticipate these newer agents will have less long-term hematologic toxicity, it remains to be proven.

4. Secondary myeloid malignancies in NHL

Similar to HL, advances in therapy for NHL over the last few decades have improved cure rates with an increasing number of long-term survivors. NHL represents a much more heterogeneous group than HL with varied treatment paradigms. While novel therapies are entering into front-line therapy for indolent B-cell malignancies, cytotoxic chemotherapy remains the mainstay for diffuse-large B-cell lymphoma (DLBCL), the most common NHL histology. Long-term data has been much more limited for NHL but is starting to emerge as the median survival improves.

As with HL, radiation fields and dosing as well as chemotherapy in NHL have changed in the last several decades. The National Cancer Institute (NCI) reported a positive correlation between cumulative radiation dose to the bone marrow and the risk of acute nonlymphocytic leukemia (ANL) [25]. In 517 NHL patients treated on various NCI protocols between 1954 and 1975, the cumulative 10-year risk of ANL was 7.9%. The risk appeared to be greatest in those receiving intensive radiation (total nodal irradiation (TNI), total body irradiation (TBI) and hemibody irradiation (HBI)). Many of the ANL patients were heavily treated with both chemotherapy and RT. Other studies have confirmed the increased risk of t-MDS/AML with TNI or low-dose TBI and postulated synergistic leukemogenic effects when combined with alkylating agents [26,27].

In one of the earliest studies, the British National Lymphoma Investigation (BLNI) extracted information on patients less than 60 years at diagnosis and treated between 1973 and 2000 to assess the risk of secondary malignancy [28]. Treatments were categorized into three groups: chemotherapy, RT and combined-modality. Sub-analyses were also conducted for the two most common chemotherapy regimens, chlorambucil, and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). In the cohort of 2456 patients, the mean age at treatment was 46.5 years, and with a median follow-up of 7.7 years, there were no cases of leukemia in the

RT only group (most received IF-RT). The RR of leukemia was similar in the chemotherapy and combined-modality groups. In CHOP treated patients, the RR of leukemia was 14.2 (95% CI, 6.8 to 26.2) vs. 19.2 (95% CI, 9.6 to 34.3) for those treated with chlorambucil. The RR for leukemia was increased for the first ten years but then decreased. Overall, the standardized incidence ratio (SIR) of t-AML was 13.1 with an EAR of 4.5. The BLNI study and others suggest that local radiotherapy alone does not increase the risk of t-MDS/AML above that associated with alkylating agents [29].

Many of the population-based studies examining secondary malignancy risk included a varied population which confounds incidence. In a large US population study, data was reported on 43,145 patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), DLBCL or follicular lymphoma (FL) treated between 1992 and 2006 with at least one-year survival after diagnosis [30]. Risk of ANL was higher after DLBCL (SIR = 4.96) and FL (SIR = 5.96) but not after CLL/SLL. In both DLBCL and FL, the ANL risk was more significant for patients diagnosed at age less than 55 years and for patients who received chemotherapy as initial treatment. Specific information on chemotherapy regimens was not available. In another study of 602 NHL patients in Copenhagen treated with chemotherapy with or without RT, the estimated actuarial incidence of ANL was 6.3 ± 2.6% at seven years [31]. In those treated with an alkylator, the estimated actuarial risk of ANL was 8% at nine years. A more recent population-based analysis of the SEER database included 18,245 NHL patients older than 65 years treated between 2001 and 2011 [32]. At a median follow-up of 3.5 years, 666 patients (3.7%) developed t-MDS/AML. Risk factors for t-MDS/AML included NCI comorbidity index scores of 2 or greater, “other” subtype NHL, stage III/IV disease, chemoimmunotherapy and administration of G-CSF. The risk of t-MDS/AML also appeared to be related to the number of G-CSF doses. On review of the literature, the actuarial incidence of t-MDS/AML with conventional chemotherapy is in the range of 5%–8% at ten years [1,29,30].

Indolent lymphomas such as FL and CLL/SLL merit special attention given their natural disease course and prolonged exposure to cytotoxic agents, particularly in younger patients. Fludarabine, a purine analog, has been used with increasing frequency. The Italian Lymphoma study group reported secondary malignancy rates in 563 patients with indolent NHL treated on studies between 1988 and 2003 [33]. At a median follow-up of 62 months, there were 12 cases of t-MDS/AML with a median time to diagnosis of 25 months (range, 6–168 months). In a multivariate analysis, fludarabine-based treatment was associated with an increased risk of secondary malignancy; however, in a univariate Cox regression analysis, fludarabine did not appear to be associated with the development of t-MDS/AML.

While fludarabine monotherapy may not clearly be related to t-MDS/AML, it has often been combined with alkylators or topoisomerase II inhibitors (anthracyclines) in the treatment of indolent NHL. In Cancer and Leukemia Group B 9011 (CALGB 9011), 544 untreated CLL were randomized to chlorambucil, fludarabine or fludarabine plus chlorambucil. With a median follow-up of 4.2 years, six patients (1.2%%) developed t-MDS/AML [34]. Five were treated on the combination arm, and one received chlorambucil alone. The probability of developing t-MDS/AML was statistically different between the three treatment groups. In the last decade, the fludarabine, cyclophosphamide and rituximab (FCR) regimen emerged as a preferred frontline treatment in younger, fit CLL patients [35]. MD Anderson cancer center (MDACC) retrospectively analyzed all patients who received FCR as frontline CLL therapy between January 2004 and March 2012 [36]. In the 234 analyzed patients, 12 (5.1%) developed t-MDS/AML at a median time of 2.7 years (range 1.1–7.8 years). The crude incidence in patients less than 60 years was 6.3% (8/127) and 3.7% (4/107) in patients 60 or older. In human CLL cell lines, fludarabine potentiates DNA damage caused by alkylating agents and subsequently inhibits DNA repair [37]. While the combination may contribute to higher response rates, it may also be an etiology of increased t-MDS/AML risk. Other NHL studies have demonstrated increased risk of t-AML/MDS with fludarabine-based combinations [35,38]. Many of the treatment paradigms in indolent NHL are shifting toward more targeted therapies and place the role of chemotherapy into question.

5. New therapies in NHL

Multiple new therapies are rapidly altering the treatment paradigms for NHL patients, particularly those with indolent disease. While most of the newer agents are targeted therapies, bendamustine, an alkylating agent, has become rapidly adopted in indolent NHL (first line and relapsed) and relapsed HL. While the drug was used exclusively in the German Democratic Republic (GDR) for 30 years, data for t-MDS/AML is relatively limited. In a retrospective cohort study, 149 patients with indolent NHL on 3 studies using bendamustine were identified [39]. At a median follow-up of 8.9 years, eight patients developed t-MDS/AML with CIR of 6.2% (95% CI 3.1–12.2%). The median time to t-MDS/AML after bendamustine was 23 months; median time to t-MDS/AML from initial diagnosis was 89 months. Lenalidomide, an immunomodulatory agent, initially approved for multiple myeloma (MM) and MDS with del(5q) has been FDA approved in combination with rituximab for relapsed/refractory mantle cell lymphoma. Excellent response rates have been reported with the “chemotherapy-free” combination in the first line setting for NHL [40]. As there is limited experience in lymphoma patients, much of the long-term toxicity data comes from the MM population. Both MDS and AML have been described in MM patients on lenalidomide [41,42]. The incidence of t-MDS/AML is complicated as many of the patients received prior alkylating agents. The role of lenalidomide and risk for t-AML/MDS remains under investigation and is explored in a companion review in this issue.

Other agents such as the BTK inhibitor, ibrutinib, are rapidly altering treatment strategies for CLL/SLL. The superiority of ibrutinib as compared to chemoimmunotherapy (FCR) has been recently reported [43,44]. Venetoclax, a bcl-2 inhibitor, has been approved for CLL with 17p deletion as well as previously treated CLL. Idelalisib, a phosphoinositide 3-kinase inhibitor, is approved for CLL and indolent lymphoma. Each of these new targeted agents has a unique toxicity profile. As single agents, they seem unlikely to increase risk of t-MDS/AML. However, as their use increases, and they are combined with cytotoxic chemotherapy, it will be crucial to continue to assess t-AML/MDS risk.

6. High-dose chemotherapy & transplant

Autologous stem cell transplant (ASCT) remains an important modality in the treatment armamentarium for patients with relapsed HL and NHL. While there is clearly a risk of t-MDS/AML after ASCT, the contribution of transplant to the risk is less certain. There have been multiple studies in the literature which are confounded by varied populations, reporting and statistical methods. Around 1994, five major medical centers including University of Minnesota Medical School, St. Bartholomew's Hospital, Dana-Farber Cancer Institute, City of Hope National Medical Center and University of Nebraska Medical Center, reported on the incidence of t-MDS/AML in NHL patients undergoing ASCT at their respective institutions [45–49]. The number of treated patients ranged from 64 to 262 with a total of 893 patients; the crude incidence of t-MDS/AML was 4.5% and ranged from 2.8% to 7.6% in the reported data. The conditioning regimens varied, but most patients were treated with chemotherapy, usually cyclophosphamide and TBI. Actuarial incidence ranged from 8% (cumulative incidence) at 7 years to 18% ± 9 at 6 years. The higher incidence rates for t-MDS/AML were initially worrisome to some but in subsequent studies, have not been born out. In one of the larger studies, the European Bone Marrow Transplantation (EBMT) Lymphoma registry examined the risk of t-MDS/AML in 131 centers representing 4998 patients transplanted between 1978 and 1996 [50]. For NHL patients, the incidence of t-MDS/AML at 2, 4 and 10 years was 0.7% (95%CI 0.4–1.2), 3.0% (CI 2.0–4.3) and 5.7% (CI 3.4–9.4). For HL patients, the incidence of t-MDS/AML was similar; at 2 years, it was 0.8% (CI 0.4–1.5) and at 5 year was 4.6% (3.1–6.8). Other studies have subsequently confirmed t-MDS/AML incidence after ASCT is similar to incidence in patients treated with conventional chemotherapy [51–53].

Given the heterogeneity in the studies, it has been difficult to assess specific risks for t-AML/MDS after ASCT for lymphoma. Several risk factors have been repeatedly identified in multiple studies including age, TBI and quantity of pre-transplant chemotherapy. Other studies have reported factors associated with abnormal stem-cell collection include lower stem cell count or increased number of days of apheresis [54]. Much of the evidence to date supports the hypothesis that pre-transplant therapy determines much of the risk for t-MDS/AML. Specific cytogenetic abnormalities that became apparent with t-MDS/AML have been identified in the ASCT product retrospectively [55,56]. It cannot be excluded that ASCT increases the risk of t-MDS. Several mechanisms have been suggested in the literature including priming chemotherapy and genotoxic damage to stem cells, the conditioning regimen and proliferative stress in the post-transplant period [57]. Careful selection of patients and minimizing leukemogenic therapies may mitigate risk of t-MDS/AML after transplant. Patients should be counseled on the risks, especially since the outcomes for t-MDS/AML are so dismal.

7. Conclusion

HL and NHL patients have an increased risk of t-MDS/AML. While multiple variables have been implicated, age, chemotherapy and extensive RT consistently emerge as risk factors for t-MDS/AML. The chemotherapy risk appears to be related to specific drugs and quantity of chemotherapy. In HL, the transition from MOPP to ABVD, with decreased alkylating agent exposure, appears to be associated with a decreased risk of t-MDS/AML. While $BEACOPP_{escalated}$ is purported to have increased risk of t-MDS/AML, it is clear that limiting patients to less than 4 cycles mitigates the risk. In NHL, it is not clear the risk in DLBCL has changed as the initial treatments have not changed significantly. However, in indolent NHL, non-cytotoxic strategies are now being employed commonly. Additional time will be necessary to assess for a decrease in t-AML/MDS risk. Overall, it appears that lymphoma therapy is getting safer. Strategies to best recognize patients at risk are ongoing and may impact treatment choices in the future.

Conflict of interest statement

None of the listed authors have a reported conflict of interest.

Practice points

- In HL, the risk of t-MDS/AML has appreciably decreased with newer regimens such as ABVD as compared to MOPP.
- In NHL, the actuarial risk of t-MDS/AML approaches 5–8% at 10 years.
- Localized radiation therapy is not significant risk factor for t-MDS/AML as compared to intensive radiation strategies.
- The risk of t-MDS/AML after ASCT is largely related to the chemotherapy strategies prior to transplant.

Research agenda

- The emergence of targeted therapies, particularly in indolent lymphoma, is expected to result in lower rates of t-MDS/AML but additional time will be needed to assess events.

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