CEBP Focus: Update on Lymphoma

Non-Hodgkin Lymphoma Secondary to Cancer Chemotherapy

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Abstract

Increased long-term survival seen in patients with solid and hematologic cancers achieved as a result of aggressive chemoradiotherapy has come at a price. Therapy-related acute myeloid leukemia has been frequently documented in these patient cohorts, and its biology well studied. Recognition of secondary non-Hodgkin lymphoma as a cause of significant morbidity and mortality in these patients is equally important. The patterns of incidence and latency of secondary lymphomas is distinct from that of myeloid malignancies and other solid cancers. We have systematically analyzed and summarized reports from various groups over the last three decades. Risk of secondary lymphomas increases after the first 5 years of completion of chemotherapy or radiotherapy and persists for more than three decades. This reinforces the need for long-term follow-up of all patients exposed to chemoradiotherapy and confirms that chemotherapeutic agents can cause lymphoma. (Cancer Epidemiol Biomarkers Prev 2007;16(3):377–80)

Introduction

Understanding the pathogenic basis of therapy-related cancers can give significant insights into the nature of the environmental exposures important in the etiology and mechanisms involved in the causation of these tumors. A group of tumors to which this approach can be applied is the non-Hodgkin lymphomas (NHL). This is a group of related tumors currently best classified according to WHO criteria. Our understanding of the environmental factors relevant to their etiology is limited, and new insights into the etiologic mechanism would be very helpful.

Pathogenesis of NHL

Lymphomas are classified by reference to their normal cellular counterparts that are involved in the immune response. By definition, they have all completed the rearrangement of their immunoglobulin genes to form a functional B cell receptor and are grouped further by their relationship to the germinal center (GC). The characteristic features of the GC response (1) are the introduction of mutation into the immunoglobulin variable region, a process called "somatic hypermutation" and "class switch recombination" (CSR) whereby the constant region of the immunoglobulin (Ig) genes is changed. A further process, which may be involved, is the presence of "receptor editing" or "VDJ recombination," but the evidence supporting the occurrence of these events at this stage of B-cell ontogeny is contradictory. GC and post-GC tumors seem to arise because of aberrations of all of these mechanisms, a major feature of which is DNA double-strand break (DSB) formation and repair. This process of aberrant Ig recombination and class switch recombination is central to the generation of the t(14;18) translocation seen in follicular lymphoma and the t(8;14) translocation typical of Burkitt lymphoma. What

follows from this is that environmental factors, which increase the likelihood of DSBs, are implicated as etiologic factors for the lymphomas.

Etiologic Factors

Despite extensive epidemiologic study, few clues to the environmental factors important in the etiology of the majority of NHL have emerged. Although specific causative links have been identified for certain subtypes of NHL, it has been difficult to generalize these to the majority of incident cases in the western world. It is likely that a characteristic of new candidates worthy of further study would be their ability to interact with and drive aberrant events generated by the processes important in normal lymphocyte biology, increasing the background rate of aberrant DSBs and the likelihood of the development of translocations and mutations. Potential mechanisms and candidates may be suggested by the study of secondary NHL (sNHL).

Secondary Cancers

The earliest report (2) of the association between hematologic malignancies and solid tumors appeared in the late 1950s. However, the link between chemotherapy and predisposition to secondary cancer was not made until two decades later, after a follow-up study (3) of over 400 cases of HL in which ~3% of patients developed secondary cancer. This study raised serious questions about the role of combined chemo-/radiotherapy in the causation of these tumors. With the availability of data on follow-up of almost three decades, it is clear that the leading cause of mortality and morbidity in this group of patients is the development of secondary cancers. A progressive rise in relative risk and actuarial excess risk of all solid tumors was noted over time, and in some studies, the actuarial excess risk of solid tumors was above 20%, with cancers of the lung, female breast, colon, and stomach being among the most common solid tumors typically occurring after the first 10 years of follow-up with rising incidence throughout the second decade. Although therapy-related acute

Table 1. Summary of studies examining the frequency of second cancers in particular secondary NHL

Authors	Year	Source of data	Primary cancer	Follow-up period	Total number of patients	Numbers of secondary cancers	Numbers of sNHL	Percentage of sNHL (%)	Relative risk
Foss et al. (15)	2002	Norwegian cancer registry	HL	1968-1985	1,024	197	31	3	24.2 (16.4-34.3)
Travis et al. (16)	1997	Multinational cancer registries	TC	1935-1993	28,843	1,406	68	0.23	1.88 (1.46-2.39)
Tucker et al. (17)	1988	Stanford University Medical Center	HL	1968-1985	1,507	98	9	0.59	0.5 (8.1-33.5)
Kaldor et al. (18)	1987	Multinational population-based registries	HL, TC, OC	1945-1984	133,411	3,157	97	0.07	1.8 (NA)
Hooning et al. (19)	2005	Netherlands Cancer Institute	BC	1970-2000	7,425	493	12	0.16	1.19 (0.61-2.08)
Henry-Amar et al. (20)	1992	International database on Hodgkin disease	HL	1960-1987	12,411	631	106	0.85	31.77 (NA)
Van Leuwen et al. (21)	1994	Netherlands Cancer Institute	HL	1966-1986	1,939	146	23	1.1	20.6 (13.1-30.9)
Swerdlow et al. (22)	2000	BNLI and other United Kingdom databases*	HL	1963-1993	5,519	322	50	0.90	14 (10.5-18.3)
Mauch et al. (9)	1996	Hospital-based	HL	1969-1988	794	72	10	1.25	18.4 (8.6-33.8)
Neglia et al. (23)	2001	CCSSG	Various	5-y follow-up	13,581	314	13	0.09	1.51 (0.80-2.58)
Bhatia et al. (24)	1996	Multicenter cancer registries	HL	1955-1986	1,380	79	6	0.43	20.9 (7.7-42.0)

Abbreviations: BNLI, British National Lymphoma Investigation; CCSSG, Childhood Cancer Survivor Study Group; HL, Hodgkin lymphoma; TC, testicular cancer; OC, ovarian cancer; BC, breast cancer; NA, data not available; sNHL, secondary NHL.
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myeloid leukemia (AML) is the most commonly occurring hematologic malignancy occurring in the first 10 years of follow-up, review of these data identified a consistent excess of B-cell NHL occurring in the first 10 years and a steadily rising incidence after that.

Secondary NHL

Krikorian et al. (4) were the first to report the increased risk of sNHL in patients successfully treated for Hodgkin disease. In a systematic analysis of published reports on the incidence of sNHL, we confirm this excess of sNHL. The data in this study were obtained through systematic searches of the literature and included several multinational and multicenter long-term survivor data from cancer registries and hospital-based studies. Hodgkin disease, testicular and ovarian cancer, which respond well to chemotherapy and radiotherapy and are associated with good long-term survivorship, offer the best setting for protracted follow-up to study this question. To avoid anecdotal reporting, studies on smaller groups and case reports were excluded. In addition, where studies were reported by the same group or center at different time points, the most recent reports were chosen. Unfortunately, there was limited information on subtypes of the NHL in most of the studies. Extensive analysis could not be undertaken to identify any specific relationships due to the different quality of information from individual registries and data collected over different time periods.

Heterogeneous and limited information on the treatment of primary cancers did not allow the interpretation of the relationship between secondary malignancy and direct effects of chemoradiotherapy on pathogenesis. A total of 207,834 patients were included. About 6,915 secondary cancers were recorded (Table 1). Of these, sNHL was diagnosed in 425 patients. Because the population size and characteristics of each study are highly variable and the proportion of sNHL in each cohort varied from 0.88% to 16.80%, the weighed average

was calculated as 5%. This is in agreement with most reports where the incidence rates varied between 0% and 5.9% (5). Compared with most secondary cancer, the incidence of sNHL is noticeably higher in patients treated for Hodgkin disease. Typically, sNHL develops after the first 5 years of initial therapy of primary cancer. There seems to be a variable period to reach peak incidence with different groups reporting cases with latent periods of 10 to 17 years post–primary therapy. The risk, however, continues to remain high after that. Cases have been reported even after 30 years of follow-up, emphasizing the need for continued patient monitoring. Although specific subtypes have not always been defined, the general consensus is that the sNHLs are often clinically aggressive, high-grade diffuse large cell tumors. These tumors often have an extranodal presentation mainly involving the gastrointestinal tract and central nervous system. Most are B-cell type, but T cell-NHL (6) also has been reported.

Pathogenesis of sNHLs

There are a number of potential mechanisms acting in the pathogenesis of sNHL, which can be inferred by a closer analysis of the data.

Link with Radiation. The association between radiation exposure and secondary malignancy in the therapeutic setting is well recognized. However, outside of this setting, there is only limited evidence for an effect of radiation in the pathogenesis of sNHL. Even among the most studied group of atomic bomb survivors in Japan, there was no evidence of an increased risk of sNHL (7). There are, however, reports of increased rates of cancer deaths in patients following radiotherapy of the spine for ankylosing spondylitis (8), but dose effects were not seen. The association of radiotherapy with sNHL is difficult to confirm, in contrast to the association with solid tumors, which is unmistakably present. In a study of HL survivors who were treated with radiotherapy alone, the actuarial excess risk

per 10,000 person-years of developing sNHL was found to be 10.6. This could be due to radiotherapy or the pathology of Hodgkin. It was noted that chemo-/radiotherapy had a greater damaging effect than radiotherapy alone, with an actuarial excess risk of 16.1 (9), but this is not always reproduced in other studies. Thus, there is weak but consistent evidence linking radiotherapy exposure to NHL. It is also a plausible association because it causes single- and double-strand DNA breaks. Thus, when lymphoid cells receive sublethal doses of radiotherapy, repair brings with it increased chances of aberrant genetic rearrangements as discussed above.

Cytotoxic Drugs. Cytotoxic drugs are clearly implicated in the pathogenesis of tAML (10) and, by implication, also in sNHL. Both alkylating agents and topoisomerase II inhibitors, implicated in tAML, may also be relevant in sNHL because they are widely used in the treatment of Hodgkin disease, from the study of which most data on sNHL are derived. A major feature of topoisomerase II inhibitors is the generation of DSBs, the repair of which can readily form substrates for inappropriate exchange. The damage caused by alkylating agents is different. The DNA lesions are complex, requiring a variety of repair mechanisms (11). Bulky alkyl groups form primary chloroethyl adducts at N and O atoms in DNA bases; these are normally repaired by O(6)-alkyl G-DNA alkyltransferase (MGMT or AGT). Secondary highly cytotoxic interstrand cross-links require nucleotide excision repair factors (e.g., XPF-ERCC1) for incision and homologous recombination to complete repair, this process may facilitate the generation of DSBs and their aberrant repair.

Accumulation of multiple DSBs leads not only to the activation of repair mechanisms but also to the activation of sensors, including ataxia telangiectasia mutated (*ATM*), ataxia telangiectasia related (*ATR*), and p53, with resultant cell cycle arrest and initiation of apoptosis or repair. The *ATM* gene, located at 11q22-23, is the primary transducer of the DSB alarm (12). Biallelic *ATM* inactivation occurs in some cases of sporadic lymphomas, supporting a role of *ATM* as a tumor suppressor gene; patients with inherited ataxia telangiectasia and an *ATM* mutation have an elevated predisposition to lymphoreticular malignancies and extreme sensitivity to ionizing radiation and other DSB-inducing agents. The catalytic processes involved in the repair of DSB are prone to error and misrepair, and chromatid exchange, with breaks occurring as a consequence of the GC reaction, may enhance the background rate of aberrant lesions.

Immunosuppression. There is little doubt that severe chronic immunosuppression and its associated immune imbalance can drive aberrant B-cell proliferation. This is most obvious in the case of the congenital immunodeficiency syndromes, which are associated with increased rates of NHL. Patients on long-term immunosuppressive therapy, as seen in the setting of solid organ transplants, are at risk of developing posttransplant lymphoproliferative disease, where immunosuppression rather than the underlying genetic defect leading to immunosuppression is inferred to be the cause for NHL. The role of ''minimal'' immunosuppression is much more difficult to quantitate. Much of our information on sNHL comes from the study of Hodgkin disease. The question that arises is whether Hodgkin disease posttreatment is associated with immunosuppression. If there is immunosuppression, it is not obvious clinically: there is no excess of infection, either bacterial or viral, compared with other, similarly treated tumors. It would seem unlikely, therefore, that the limited amount of immunosuppression seen in treated Hodgkin disease influences the development of sNHL.

Is sNHL Part of the Natural History of Hodgkin Disease?

A final consideration before firmly associating chemo-/radiotherapy with the risk of sNHL, is whether sNHL is part of the natural history of Hodgkin disease. Lymphocyte-predominant Hodgkin disease represents about 5% of all Hodgkin disease and has a distinct natural history. Following treatment, at relapse, the transformation to large B-cell lymphoma is well described and does not relate to treatment (13). This is not true for cases of classic Hodgkin disease. There is a small possibility, however, that sNHL could represent relapse from a Hodgkin disease precursor cell. Hodgkin disease is the result of a crippling mutation within the Ig genes during an abortive GC reaction (14). Studies of rare cases of concurrent Hodgkin disease and follicular lymphoma has identified GC B cell as the common progenitor, with the Hodgkin and NHL clone carrying both shared and distinct somatic mutations.

Whether the presence of an underlying precursor cell is a unifying mechanism is currently uncertain. However, the analysis of sNHL arising from the treatment of other tumor types can answer this question. We have looked at a number of tumor types to address this issue. Long-term survivors of testicular cancers have a notable increase in the incidence of sNHL. In these instances, there is no common precursor cell, and sNHL must be the consequence of damage occurring because of the therapy, i.e., tNHL. The standard form of treatment for these cancers consists of orchidectomy and local radiotherapy or chemotherapy, implicating exposure to these in the pathogenesis of sNHL. There are a number of cancer genes unique to breast cancer, and a subset of these patients seem to have increased rates of sNHL. Therefore, whereas relapse from a precursor cell may explain some cases of sNHL in Hodgkin disease, the common unifying exposure is chemotherapy.

Conclusion

Exposure to chemotherapy and radiotherapy results in single- and double-stranded breaks and interstrand cross-links. There are a number of mechanisms leading to the repair of these lesions that may interact with the normal GC mechanisms to increase the risk of aberrant recombination events and malignant transformation. The agents that cause this damage, alkylating agents, topoisomerase inhibitors, and radiotherapy, all cause these lesions. In conclusion, therapeutic agents used in the therapy of primary cancers causing DSBs may be implicated as causal factors in the etiology of sNHL.

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