The treatment of lymphoma complicating autoimmune disease: two birds with one stone?

Lymphoproliferative diseases, particularly non-Hodgkin’s lymphoma (NHL), have increased dramatically in frequency during the last three decades with a more than two-fold increase in NHL incidence from the mid-1970s to the mid-1990s alone. NHL is currently the fifth most common malignancy in the USA with ~60 000 new cases diagnosed annually. Although environmental and genetic risk factors for lymphoma are not well defined, antecedent autoimmune disease has been increasingly recognized as a robust determinant of NHL risk. Rheumatoid arthritis (RA), a systemic autoimmune condition characterized by synovial inflammation and progressive joint deformity, has been associated with a two- to six-fold increase in the risk for NHL (reviewed in [1]). Relative risks for lymphoproliferative disease may be even higher in conditions such as systemic lupus erythematosus (SLE) and Sjogren’s syndrome (reviewed in [2]).

Despite much needed insight provided by recent investigations, the precise etiology of NHL in the context of autoimmune disease remains poorly understood. It has long been hypothesized that disease-modifying antirheumatic drugs (DMARDs) and other immunomodulating agents used to treat these conditions are major culprits or at least play an important role in heightening the overall risk for lymphoproliferative disorders. There have been numerous reports, for instance, indicating an association of methotrexate (the ‘gold standard’ DMARD for the treatment of RA) with incident NHL, particularly with tumors positive for Epstein–Barr virus (reviewed in [1]). Likewise, cyclophosphamide (a commonly used intervention in systemic vasculitis and the treatment of end organ complications of SLE) has been associated with subsequent development of lymphoproliferative diseases including NHL. Concerns regarding the role of DMARDs and immunomodulators used to treat rheumatic conditions and NHL risk have been fueled by reports indicating associations of biologic therapies (particularly those targeting tumor necrosis factor-α) with lymphoma development [3]. Taken together, reports linking both conventional and biologic DMARDs with lymphoproliferative diseases have been a major source of angst for patients suffering from autoimmune disease as well as health care providers.

In this issue of the *Annals of Oncology*, Wohrer et al. [4] provide results from a select case series of patients with varied autoimmune conditions complicated by NHL and receiving standard treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). As detailed by the authors, their results—although preliminary in nature—indicate that R-CHOP has dual efficacy in the treatment of both NHL and the underlying autoimmune disease, perhaps circumventing the need for ‘high-risk’ DMARDs and, in the process, alleviating patient and provider angst.

While the report by Wohrer et al. [4] is intriguing, there are important limitations to this work that warrant discussion. Most notably, the heterogeneous makeup and small size of this retrospective cohort greatly limit inferences that can be drawn from this effort. Given the nuances of different autoimmune conditions and anticipated differences in responses to immunomodulating therapies, combining these cases in a single analysis may be problematic. Small sample sizes and resulting limits in statistical power are not unique to this study and are perhaps the single greatest barrier to conducting research in this area. We recently reported on our own experiences with a systematic evaluation of a large tissue registry of subjects with lymphoma [5]. Examining the records of >3000 NHL cases collected during a 20-year time span, we were able to identify only 24 cases with either definite or probable RA. In a national French study examining the association of methotrexate use with incident lymphoma, investigators identified only 18 cases of incident NHL meeting inclusion criteria during a 3-year period of follow-up [6].

In addition to problems of heterogeneity and small sample size, the accompanying retrospective report appears to rely on self-reported diagnoses for autoimmune conditions rather than validated disease classification criteria (i.e. American College of Rheumatology or ACR classification criteria for RA [7] or SLE [8]), potentially problematic given the limited predictive value of the former approach. Similarly, the efficacy analyses relevant to the underlying connective tissue diseases are based solely on serial patient ‘global’ reports rather than more universally accepted and validated composite measures of disease activity that are available and widely used both as research tools and in the clinic, measures such as the disease activity score in RA that combines patient-level data (global well-being) with more objective measures including tender and swollen joint counts and values of acute-phase reactants [9].

As the authors concede, it should perhaps not be too surprising that R-CHOP would prove efficacious in the treatment of autoimmune disease, conditions characterized by the presence of autoreactive lymphocytes. Rituximab, a chimeric monoclonal anti-CD20 antibody that targets and depletes B cells, has revolutionized the treatment of NHL and has recently been approved in both Europe and the USA for the treatment of RA and is under active investigation for the treatment of SLE. There are numerous reports indicating that
rituximab may be efficacious in the treatment of other autoimmune diseases including, but not limited to, systemic vasculitis [10] and Sjögren’s syndrome [11]. Glucocorticoids and cyclophosphamide are the cornerstones of treatment in select rheumatic conditions and important adjuvant therapies in others. Given its potent ‘lymphotoxic’ effect, it is conceivable that CHOP therapy alone, even in the absence of rituximab, would prove efficacious in the treatment of select autoimmune diseases. Although rituximab has been well tolerated in the background of CHOP therapy in NHL, care must be taken in extrapolating these data to connective tissue diseases. Recent reports of progressive multifocal leukoencephalopathy occurring with the use of rituximab in the treatment of SLE [12] warrant caution and continued vigilance with ongoing clinical trials and postmarketing surveillance in autoimmune disease.

For the reasons noted above, it should also perhaps not be too surprising that R-CHOP leads to substantial declines in autoantibody concentrations, including dramatic declines observed in this study in both rheumatoid factor (RF) and antinuclear antibody (ANA). It is important to note, however, that declines in these autoantibody values do not necessarily translate into clinical efficacy and are not currently components of validated measures of disease improvement in RA, SLE, or other connective tissue diseases. It is noteworthy that studies examining the use of rituximab in autoimmune conditions have shown that declines in disease-specific autoantibodies (including RF, ANA, and others) appear to be disproportionate from changes in total immunoglobulin levels [13], indicating that autoreactive B cells may serve as preferential targets with this approach.

The accompanying report provides other interesting observations warranting discussion. In this report [4], investigators observed a median response duration of just 7 weeks. This is somewhat surprising given the relatively durable responses that have been seen in RA and other conditions with similar treatment strategies [10, 13, 14]. Perhaps the closest comparison to R-CHOP investigated for the treatment of an autoimmune disease comes from an open-label study comparing the use of rituximab in combination with either cyclophosphamide or methotrexate versus methotrexate alone (control) in the treatment of refractory RA with background therapy that included high-dose glucocorticoids [14]. In this study, 41% of subjects receiving a single treatment course with the combination of rituximab and cyclophosphamide (versus 13% with methotrexate alone) had 50% improvement based on the composite ACR criteria [15] at 24 weeks, an effect that was maintained after 48 weeks of follow-up. The abbreviated response duration observed in the study by Wohrer et al. [4] coupled with known pharmacokinetic data (showing declines in rituximab concentrations after 2–3 months) indicate at first glance that rituximab dosing may need to be repeated in this population at 2- to 3-month intervals in order to be effective for treatment of the underlying autoimmune condition. Such a recommendation, however, is premature and strongly conflicts with current practice relevant to rituximab use in autoimmune disease. At present, the standard dosing interval for rituximab in autoimmune disease is 6 months or longer, an interval that has been based on data from well-designed clinical trials and from concerns over B-cell depletion and possible hypogammaglobulinemia. Following a single treatment with rituximab in RA, B-cell numbers remain profoundly depressed for periods as long as 6–18 months [13, 14]. Although a single course of therapy does not appear to lead to significant hypogammaglobulinemia, the effect of repeated courses of rituximab and the potential longer term consequence of immunoglobulin deficiency (i.e. infection) remain unknown.

Of the 13 NHL cases observed in this series, nine (69%) were mucosa-associated lymphoid tissue (MALT) subtypes, far in excess of the expected frequency for this relatively uncommon (<2%–5% of NHL tumors in most series) subtype in the general population. An increase in low-grade MALT subtypes, however, has been reported in select autoimmune conditions including Sjögren’s syndrome (reviewed in [2]) and Hashimoto’s thyroiditis (reviewed in [2]). In the accompanying series, MALT subtypes were observed in four of six RA cases. This is in contrast to two much larger cohorts of RA patients with secondary NHL in which MALT represented between 1% [16] and 5% [17] of all subtypes observed. Given the small number of RA patients included in the present series, this may simply reflect chance. Alternatively, it is possible that these RA patients had overlapping Sjögren’s syndrome, an extraarticular RA feature with a cumulative incidence of ~10% [18]. Of the four RA cases with MALT, two had their lymphoma diagnosed before the onset of their connective tissue disease, raising the possibility that articular complaints manifesting as part of a paraneoplastic syndrome are perhaps a frequent feature of this lymphoma subtype. It is worth noting that all nine cases of MALT in this series represented recurrent NHL.

The prevalence of seropositivity for both RF (five of nine) and ANA (eight of nine) among patients with autoimmune disease and MALT has led to the conclusion that it would be reasonable to measure autoimmune parameters on a ‘routine basis in patients with NHL’ as a screen for underlying rheumatic disease, a recommendation not well founded on the basis of the evidence provided. In this series, only two of the 13 subjects examined had their connective tissue disease diagnosed subsequent to NHL and only one of these subjects, respectively, was positive for RF or ANA. In the absence of an appropriate comparator group (i.e. subjects with NHL and no evidence of a connective tissue disease), the metric properties of these assays in this specific population remain unknown. In the absence of such data, it is difficult to recommend routine measurement of RF or ANA, particularly when these assays are known to have limited predictive value in the general population when the pretest probability is low and consequences of false-positive and false-negative tests are not well known. Clearly, additional studies examining the utility of RF and ANA in this population, in addition to other autoantibodies with perhaps more optimal predictive values (i.e. antibody to cyclic citrullinated peptide in RA), would prove valuable.

While additional studies are clearly needed, there have been important recent gains in our understanding of NHL-related outcomes and risk factors as they pertain to autoimmune diseases. In a seminal study by Baecklund et al. [16], for instance, increased NHL risk in RA was limited to subjects in the highest decile of RA disease activity. Compared with those
with low disease activity, patients with high disease activity had >70-fold increased risk for lymphoma (odds ratio (OR) 71.3; 95% confidence interval (CI) 24.1–211.4). This is consistent with prior reports revealing associations with elevated acute-phase reactants and extraarticular disease manifestations with lymphoma risk in RA [19, 20]. Notably, these investigators found no evidence of associations of DMARD use with lymphoma risk, indicating that unchecked systemic inflammation is the primary trigger for lymphoproliferative complications observed in RA [16]. Consistent with findings from our group [17], Baecklund et al. [16] found that diffuse large B-cell (DLBC) lymphoma was the most frequent NHL subtype, accounting for 48% of lymphomas occurring in RA. Of the DLBC cases examined, more than two-thirds had a nongerminai cell phenotype [21], a proportion significantly higher than that observed in non-RA populations; thus indicating a more aggressive lymphoma phenotype in the context of RA.

Somewhat counter to these results, we recently found that subjects with RA and NHL had improved lymphoma-related outcomes compared with non-RA controls with NHL [17]. Although RA patients with NHL had a similar overall survival compared with non-RA subjects, these patients were at lower risk for lymphoma progression/relapse (OR = 0.41; 95% CI 0.25–0.68) or death related to lymphoma or its treatment (OR = 0.60; 95% CI 0.37–0.98). On the surface, these findings appear to be consistent with those of Wohrer et al. [4]. Of 13 subjects in this study, 11 experienced a complete remission of their lymphoma and the remaining two had a partial remission with standard R-CHOP therapy. In our study, we also found that RA patients compared with controls had greater mortality from causes unrelated to lymphoma or its treatment (including cardiovascular disease), essentially negating any positive impact from having more indolent tumor phenotypes. It is possible that any differences in our study (follow-up, 1984–2002) with that of Baecklund et al. [16] (follow-up, 1964–1994) may relate to different time frames examined and differences in DMARD use, with ~70% of subjects receiving DMARDs in the ‘earlier’ study by Baecklund et al. [16] versus 95% with DMARD use in our study. While speculative, these results indicate that aggressive RA treatment, effectively lowering systemic inflammation, may decrease lymphoma risk and in cases of incident lymphoma may lead to a more indolent tumor phenotype. In addition, our results indicate that when the natural course of autoimmune disease (at least in the case of RA) is complicated by lymphoma, it is important to recognize that other comorbid diseases (i.e. cardiovascular disease) make important contributions to overall morbidity/mortality and should be addressed as part of a comprehensive treatment approach.

Similar to NHL developing in the context of RA, DLBC is the most common lymphoma subtype to develop in the context of SLE. Of 42 SLE patients with NHL in a recent report by Bernatsky et al. [22], 22 subjects had died a median of only 1.2 years after lymphoma diagnosis, indicating a particularly aggressive lymphoproliferative disease in this group. While SLE appears to lead to a more aggressive NHL phenotype, SLE-related features that increase lymphoma risk remain poorly defined. In contrast to the case of RA or SLE, more indolent MALT subtypes appear to be more commonly observed in the context of Sjögren’s syndrome (reviewed in [2]). Similar to RA, NHL risk appears to be most pronounced in those with severe underlying autoimmune disease; in the case of Sjögren’s syndrome, disease manifested by features including severe parotid enlargement, hypocomplementemia, and cutaneous vasculitis (reviewed in [2]). In addition to the conditions discussed, lymphoma risk appears to be increased in other autoimmune diseases including Hashimoto’s thyroiditis (thyroid MALT lymphoma) and celiac disease with perhaps less clear-cut associations reported in conditions including polymyositis/dermatomyositis, inflammatory bowel disease, psoriasis, seronegative spondyloarthropathy, scleroderma, Paget’s disease, and sarcoidosis.

The issue of how to best treat NHL in the context of autoimmune disease is clearly a vexing and important question and the study by Wohrer et al. [4] represents an important initial step in that direction. Rituximab, a key component of R-CHOP and an emerging therapy for connective tissue disease, represents a potentially important addition to the treatment armamentarium for this population. Whether this therapeutic strategy (or others sure to evolve) represents ‘the single stone felling two birds’ remains to be seen. Recent strides in our understanding of lymphoma-related outcomes and epidemiology, particularly in the context of RA, SLE, and Sjögren’s syndrome, will hopefully lead to further refinements in our approach to this difficult clinical problem.

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