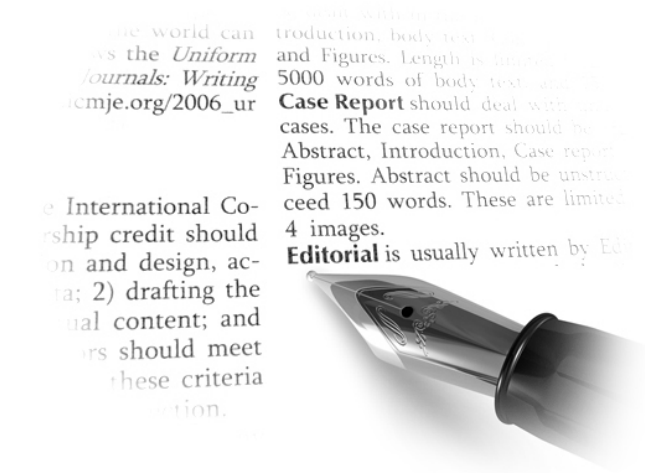

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Editorial

Low-grade lymphoma: Beyond fludarabine-single therapy

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Most patients with low-grade non-Hodgkin's lymphoma (NHL) present with disseminated disease, although many are asymptomatic at diagnosis. Several initial approaches have been used to treat such patients, but none of the treatment options have resulted in long-term disease-free survival in majority of these patients. Although some patients may achieve complete remission (CR), the remission is short-lived and usually followed by a relapse. Therefore, the prognosis for patients with indolent lymphoma (median survival, 8-10 years) has not improved much over time [1]. However, recent survival data for patients with advanced indolent lymphoma suggest that the overall survival (OS) rate has improved over the last 25 years, probably because of sequential application of different chemotherapy regimens, use of biologic agents, and improved supportive care.

Conventional therapy for low-grade NHL involves monotherapy with an alkylating agent (chlorambucil or cyclophosphamide) or administration of alkylating agents in combination with or without anthracyclines (cyclophosphamide, vincristine, and prednisone or cyclophosphamide, vincristine, prednisone, and doxorubicin), depending on the clinical aggressiveness of the disease. The unsatisfactory results observed in terms of CR and long-term disease control led to the therapeutic investigation of purine analogues in this disease subset.

The past decade has witnessed the emergence of fludarabine as an active agent for low-grade NHL treatment. Although early trials with single-agent fludarabine showed response rates of 30-50% in previously treated patients, recent efforts have focused on combining fludarabine with other agents, especially mitoxantrone [2, 3] and cyclophosphamide [4]. Clinical trials with these combination regimens have reproducibly yielded overall response rates of 60-90% [5].

The use of fludarabine, mitoxantrone, and dexamethasone (FND) induced a response rate of 94%, with a CR rate of 46% (duration of CR [median], 21 months). Although FND was well tolerated, many patients developed myelosuppression and opportunistic infections including *Pneumocystis carinii*, herpes zoster, and mycobacterial infections. The potent antilymphocytic activity of fludarabine, particularly for T cells, has been incriminated for this effect. Similar toxicities were reported in chronic lymphocytic leukemia (CLL) patients treated with fludarabine: addition of corticosteroids increased opportunistic infections without inducing significant antitumor effects.

The fludarabine and cyclophosphamide (FC) combination has been extensively studied for the management of CLL patients. FC was used as the first-line treatment and was associated with high rates of objective response (86-100%) and CR (20-60%). These results have been recently confirmed by 3 phase III studies, in which FC was compared with fludarabine and chlorambucil. The major toxicity in these studies was hematological: grade IV neutropenia associated with severe drug-related lymphopenia caused a substantial rate of infectious complications. The most important complication after myelosuppression was early appearance of second tumors at the follow-up. Therapy-related myelodysplasia (tMDS) and therapy-related acute myeloid leukemia (tAML) are well-known complications of combination

regimens of fludarabine and alkylating agents. Nearly 10% of lymphoma patients treated with standard chemotherapy develop tMDS/tAML. FC regimen may increase the risk of tMDS/tAML probably because of their synergistic effects of induction and inhibition of DNA repair following DNA damage [6].

Recently, immunochemotherapy with rituximab (chimeric anti-CD20 monoclonal antibody) has shown impressive response rates and prolonged progression-free survival in patients with indolent lymphomas [7]. There are 2 possible explanations for the survival advantage with rituximab-chemotherapy (R-chemo): patients treated with R-chemo may have higher initial response rates and/or prolonged disease control than that shown by patients treated with chemotherapy alone. The efficacy of rituximab as a single-agent therapy was originally established in a pivotal study performed in 166 patients with refractory or relapsed indolent B-cell NHL; the overall response rate was 48%. Early preclinical data suggested rituximab augments the sensitivity of tumor cells to cytotoxic drugs. R-chemo antilymphoma activity reflects different modes of action and the ability of the antibody to modify molecular signaling pathways. The latter is associated with decreased expression of antiapoptotic gene products (bcl-2 and bcl-xL) and sensitization of drug-resistant B-cell NHL cells to chemotherapy. However, there is no clarity on the contribution of these mechanisms to the cytotoxicity of rituximab and *in vivo* relevance of these pathways in follicular or mantle cell lymphoma patients. The impact of rituximab maintenance treatment in OS is one of the most important aspects for patients with indolent NHL. Randomized trials carried out by GLSG (German Low Grade Lymphoma Study Group) and EORTC (European Organization for Research and Treatment of Cancer) have shown that rituximab maintenance therapy after immunochemotherapy [8, 9] and after chemotherapy [8] leads to better outcomes than those achieved after post-therapy monitoring alone. The difference in OS between patients treated initially with immunochemotherapy or chemotherapy alone followed by rituximab maintenance therapy, might be minor in current and future practice.

Some new data is available on bortezomib and bendamustine combination therapy for follicular lymphoma. Proteasome inhibitors such as bortezomib have broad-spectrum activity against cancer cells, including inhibition and modulation of nuclear factor κB activity, and modification of cell-cycle and pro- and antiapoptotic pathways. In multiple phase II studies, bortezomib showed variable activity when used as a single-agent against follicular lymphoma. The overall response rate was 16-41%, with few CRs. Bortezomib may potentiate the cytotoxicity of other chemotherapy drugs. These findings have prompted further investigation of different chemotherapy regimens combining bortezomib with rituximab in follicular lymphoma patients [10].

Although this article describes an important study of fludarabine-containing regimen for Korean patients with indolent lymphoma, this study has some limitations because of insurance. A variety of chemotherapy regimens (FND, FC, and FC with rituximab) were administered in the cases included in this analysis. On the basis of the currently available data, I cannot comment on the best first-line chemotherapy regimen or the optimal number of chemotherapy cycles needed to treat patients with indolent lymphoma.

Further prospective randomized trials are required to determine the best first-line chemotherapy regimen for indolent lymphoma patients, and separate and adequately powered trials are needed for untreated patients and patients with relapsed or refractory indolent lymphoma. New combination regimens, such as bortezomib, bendamustine, and rituximab, should be evaluated in cases of other histological subtypes of indolent lymphomas.

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