Rituximab Maintenance in Indolent Lymphoma: Indications and Controversies

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Over the past few years it has been shown in previously untreated and relapsed/refractory follicular lymphoma that rituximab maintenance has a clear clinical benefit after induction with rituximab plus chemotherapy, chemotherapy alone, or rituximab monotherapy. However, the optimal dose, schedule, and duration of rituximab maintenance therapy still need to be established. The important issue of maintenance treatment versus retreatment upon relapse is the topic of the ongoing large randomized phase III Rituximab Extended Schedule or Retreatment Trial (RESORT). Current data indicate that rituximab maintenance can be safely administered for up to 2 years, although assessment of long-term safety requires longer follow-up.

Introduction
Although recent advances in the treatment of indolent non-Hodgkin’s lymphoma (NHL), of which the majority of cases are follicular lymphoma (FL), have improved the outlook for many patients, at present no proven curative treatment exists. Thus far, the course of FL has been characterized by initial responsiveness to single-agent or combination chemotherapy, with good response rates but frequent relapses. After the initial relapse, the response rate and relapse-free survival steadily diminish, resulting in a median survival of 4 to 5 years after first relapse [1]. Transformation to an aggressive lymphoma subtype can occur at any stage of the disease and is associated with a very poor prognosis [2]. In the absence of a curative treatment, nontoxic strategies for extending the duration of remission, postponing the need for subsequent chemotherapy, and, one hopes, improving overall survival (OS) are eagerly sought.

Maintenance schedules with single-agent chemotherapy and combination chemotherapy have been explored. In a randomized study conducted in 111 patients in complete remission (CR) following induction therapy, maintenance chemotherapy with bischloroethylnitrosourea (BCNU)/BCVP (BCNU, cyclophosphamide, vincristine, and prednisone) administered every 6 weeks for up to 18 months significantly improved median progression-free survival (PFS) compared with no further treatment and observation alone (P=0.02) but failed to provide any significant survival benefit [3]. In another study, patients with indolent NHL in remission after cyclophosphamide, vincristine, and prednisone (CVP) plus radiotherapy induction were randomly assigned to intermittent chlorambucil maintenance for up to 2 years or to observation alone. Chlorambucil maintenance significantly prolonged relapse-free survival compared with observation alone (P=0.045) but failed to show any significant benefit in OS [4]. In addition to the lack of demonstrable survival benefit, maintenance chemotherapy also raises concerns regarding long-term toxicities and potentially increases the risk of secondary leukemias and myelodysplasias.

Several clinical trials have addressed the use of interferon (IFN)-α2 as maintenance therapy, yielding conflicting results. In a clinical trial involving 98 patients with indolent NHL who achieved a CR after conventional chemotherapy induction, patients randomized to IFN maintenance administered three times weekly for up to 1 year achieved significantly longer remission duration (P<0.001) and median OS (P<0.001), compared with patients randomized to observation alone [5]. In contrast, in other randomized trials conducted in patients with indolent NHL, IFN maintenance after chemotherapy induction did not produce a significantly longer time to progression (TTP), PFS, or OS compared with observation alone [6–9]. Because of these conflicting results, a meta-analysis of 10 phase III studies involving 1922 patients was conducted to evaluate the role of IFN in the treatment of newly diagnosed FL [10••]. The authors concluded that a survival advantage was seen when IFN was combined with induction chemotherapy but not when IFN was given as maintenance therapy after chemotherapy induction. Moreover, as Rohatiner et al. [10••] have noted, the toxicity of IFN necessitated a considerable fraction of patients to discontinue treatment, also raising questions about its suitability in the maintenance setting.
The chimeric anti-CD20 monoclonal antibody rituximab was originally used as monotherapy for the induction of remission in patients with relapsed indolent lymphoma [11] and was subsequently combined with chemotherapy as induction therapy for patients with indolent lymphoma in the first-line and relapsed/refractory settings. Its mechanism of action involves complement-dependent cytotoxicity, antibody-dependent cytotoxicity, and direct induction of apoptosis. Over the past few years, rituximab has been increasingly used as maintenance therapy in NHL and thus far has yielded very encouraging results. A number of characteristics make rituximab attractive for maintenance therapy. First, rituximab is associated with only minimal acute toxicity, and no major long-term or cumulative toxicity has yet been described. In addition, although in the late 1990s there were a few reports on loss of CD20 expression after rituximab therapy [12,13], the CD20 target generally persists on residual or recurrent lymphoma cells, allowing for successful retreatment. Finally, the long half-life of rituximab enables infrequent maintenance treatments while still maintaining long-term drug exposure, which, in principle, could control residual malignant cells and delay disease recurrence. This infrequent administration in an outpatient setting is, of course, very relevant from the perspective of the patient.

The purpose of this article is to review the data that have emerged from key trials of rituximab maintenance therapy in patients with FL. Although some of these trials allowed inclusion of patients with different types of indolent lymphoma, the vast majority of patients had FL. Where possible, the data presented are restricted to patients with FL because, in our opinion, overall analyses of mixed cohorts of patients—with, for example, FL and chronic lymphocytic leukemia or FL and mantle cell lymphoma (MCL)—are not very meaningful. In addition, in most of these studies, the non-FL subgroups were too small to allow definite conclusions to be drawn.

### Rituximab Maintenance Treatment

The use of rituximab maintenance therapy in patients with indolent NHL has been explored following induction treatment with single-agent rituximab, combination chemotherapy, or immunochemotherapy (Table 1). These trials are discussed briefly in the following text.

A small phase II trial of rituximab maintenance therapy after rituximab monotherapy induction has been conducted in 62 patients with previously untreated indolent NHL (61% FL, 39% small lymphocytic lymphoma [SLL]) by the US-based Minnie Pearl Cancer Research Network. The study evaluated the safety and efficacy of four once-weekly 375-mg/m² doses of rituximab induction followed by rituximab maintenance for patients with CR, partial remission (PR), or stable disease at week 6 after induction [14]. The maintenance schedule consisted of four once-weekly rituximab infusions repeated at 6-month intervals for up to 2 years. At week 6, objective responses (ORs) or stable disease were noted in 28 of 60 (47%) and 27 of 60 (45%) evaluable patients, respectively; these patients were eligible to receive maintenance therapy subsequently. Of these eligible patients, 46 received at least one course of rituximab maintenance. Sixteen of 27 patients (59%) who initially achieved stable disease at week 6 achieved ORs with rituximab maintenance; overall, 25 patients (42%) improved their initial response category as a result of maintenance therapy, producing final OR and CR rates of 73% and 37%, respectively [14]. At a median follow-up of 55 months, median actuarial PFS for the overall cohort was 37 months, with a 5-year actual PFS rate of 34% [15]. Median PFS was significantly longer in patients with FL than in those with SLL (52 vs 31 months; \( P=0.04 \)), and the actuarial 5-year OS rate (overall cohort) was 70%. Rituximab induction was well tolerated, and rituximab maintenance was not associated with any grade III/IV toxicity [15].

The phase III Swiss Group for Clinical Cancer Research (SAKK) 35/98 trial was initiated in January 1998.