Chemo-immunotherapy for hairy cell leukemia

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Abstract

With the introduction of the nucleoside analogs cladribine and pentostatin the treatment of patients with hairy cell leukemia (HCL) has been revolutionized, and the majority of patients achieve a long-lasting complete remission with rare patients ever needing the traditional treatment strategies such as splenectomy. However, in the studies employing either of these nucleoside analogs, a proportion of patients do not respond to the initial therapy and the event-free survival curve does not reach a plateau, with up to 40% of patients relapsing within a few years. New therapeutic modalities including monoclonal antibodies such as rituximab and immunotoxins such as BL22 are now available. Furthermore, progress in the identification of minimal residual disease (MRD) using consensus primer or patient specific polymerase chain reaction for the immunoglobulin heavy chain variable region gene (*IGHV*), as well as multiparameter flow cytometry, allows for the detection and eradication of MRD. Whether this will translate to a reduction in the rate of relapse will require large prospective randomized trials. Alternatively, it may be possible to identify patients who are more likely to relapse using pretreatment characteristics such as the mutational status of *IGHV* and apply these strategies solely to them.

Keywords: *cladribine, rituximab, minimal residual disease, hairy cell leukemia*

Introduction

The treatment of patients with hairy cell leukemia (HCL) has changed dramatically over the last few decades. Splenectomy, historically the prime modality of treatment, is now relegated to rare instances in multiply refractory patients, and initial therapy with the nucleoside analogs cladribine and pentostatin results in complete response (CR) rates of 80–90% [1,2]. However, up to 40% of patients relapse after a follow up of 3–4 years, with little difference between the two drugs in achieving and maintaining a response [3]. Clearly, the quality of the initial response can predict its duration, being longer in those achieving a CR rather than lesser responses [4]. Therefore, we and others have undertaken efforts to identify and eradicate minimal residual disease (MRD) after the initial therapy [5].

Wheaton and colleagues noted that detection of MRD by immunohistochemistry in paraffin-embedded bone marrow sections of patients with HCL

in CR after receiving cladribine was predictive of relapse [6]. More sensitive methods of MRD detection such as immunophenotyping by flow cytometry and polymerase chain reaction (PCR) of consensus primer or clone specific immunoglobulin heavy chain genes have been evaluated recently, and can be used to monitor the disease course [5,7]. However, the importance of MRD detection and eradication continues to be a subject of discussion, with reports of long-term remission in patients with persistent MRD and even morphological evidence of HCL [8].

Cladribine followed by rituximab for treating hairy cell leukemia

We have conducted a clinical trial in which patients with newly diagnosed HCL or those relapsing after one prior course were treated with cladribine 5.6 mg/m² intravenously over 2 h daily for 5 days followed by, approximately 28 days later, eight

weekly doses of rituximab 375 mg/m². Bone marrow examination was conducted prior to the initiation of therapy, 1 month after cladribine prior to the initiation of rituximab, and after the completion of treatment with rituximab to assess for any evidence of MRD by flow cytometry and consensus primer PCR (Figure 1). We elected to allow the inclusion of patients with the variant form of the disease (HCLv), a group previously reported to be resistant to therapy with the nucleoside analogs [9].

To date, we have treated 43 patients with HCL, including 31 patients with newly diagnosed disease, five with HCLv, and seven with relapse after one prior therapy (which included cladribine in six patients and chlorambucil in one patient). All 43 patients have achieved CR after the completion of treatment with rituximab. With a median follow-up of 26 months (range, 5–68), the median CR duration has not been reached (range, 3–66 months), and only one patient (with HCLv) has relapsed. This patient was the only one dying from disease-related causes; two others died from unrelated malignancies (metastatic lung cancer and pancreatic cancer).

There was no severe, or unexpected, toxicity and no grade 3 and 4 non-hematological toxicity related to therapy. Fourteen patients had 17 episodes of reversible grade 3 and 4 infections including neutropenic fever, cellulitis, and herpes zoster. Other adverse events were grade 1 and 2 and included nausea, rash, fatigue, weight loss, and fever. Although there was a significant decline in the number of CD4 lymphocytes and immunoglobulin G after the treatment in all patients, this was not associated with a significant increase in the incidence of opportunistic infections.

Monitoring minimal residual disease

Using multiparameter flow cytometry, MRD was positive in 89% of evaluable patients in bone marrow specimens obtained approximately 1 month after therapy with cladribine, and became negative in 76% of evaluable patients after the completion of treatment with rituximab. MRD by consensus primer PCR was positive in 62% of evaluable patients after treatment with cladribine and became negative in 71% of evaluable patients after rituximab. Specimens for the evaluation of MRD by flow cytometry were

available in selected patients during the follow-up period and have remained negative in the majority. In the rare instances of conversion from a negative to a positive, this has not been associated with a morphological relapse.

Discussion

Rituximab is a monoclonal antibody against the pan-B cell antigen (CD20), which is brightly expressed on the surface of hairy cells. Several prior reports have demonstrated the significant but limited activity of rituximab in patients with relapsed and newly diagnosed HCL [10]. The relatively low toxicity of rituximab makes it an ideal agent for the potential eradication of MRD in the post-response setting, and a number of trials in other low-grade lymphoproliferative neoplasms have clearly demonstrated its potential role in extending relapse-free survival [11]. The main concern when combining rituximab with nucleoside analogs has been whether the combination will lead to an increase in the extent of immunosuppression that is already well-characterized with therapy with cladribine and pentostatin. However, prior experience in chronic lymphocytic leukemia (CLL) and follicular lymphoma has demonstrated the safety of this approach.

In the present trial, we have demonstrated the feasibility, safety, and high efficacy of the combination of cladribine followed by rituximab. Of significant interest is the achievement of CR by all patients with HCLv, suggesting a potentially important strategy in this group of patients who are typically resistant to nucleoside analogs. Prior anecdotal reports have previously suggested the efficacy of rituximab in treating this disease [12]. With a median follow-up of 26 months (range, 5–68), no patient with HCL and only one patient with HCLv has relapsed, suggesting the potential durability of these responses. However, in view of the recent reports suggesting the persistence of MRD or even morphologically detectable bone marrow disease in patients alive and well several years after the initiation of therapy, a major socio-economic consideration that needs to be considered is whether all patients with newly diagnosed disease should be treated with the combination. Recent reports have identified patients with HCL with unmutated immunoglobulin heavy chain variable gene (*IGHV*) and those with VH4-34 *IGHV* gene rearrangement as being more likely to have a suboptimal response and shorter CR duration after initial therapy with cladribine [13,14]. An alternative strategy would be to target only these and other patients identified as having a high risk for relapse by pretreatment characteristics for the combination chemo-immunotherapy.

Figure 1. Treatment schema. BM, bone marrow; C, cladribine; R, rituximab.

Another question is whether concurrent or sequential therapy is the correct strategy to incorporate monoclonal antibody therapy into the management of HCL. In a randomized phase II study by the Cancer and Leukemia Group B (CALGB) in patients with CLL, a higher overall and complete response rate was reported for the group receiving concurrent rituximab and fludarabine as opposed to those receiving the same drugs sequentially [15]. However, at the time of the report, the median response duration or survival had not been reached for either arm of the study. Patients receiving the concurrent treatment had a higher incidence of grade 3 and 4 neutropenia. More recently, Else and colleagues have reported a high response rate in patients with relapsed HCL receiving concurrent rituximab and a nucleoside analog [16]. These data suggest that the concurrent strategy may potentially be more effective in inducing and maintaining CRs, perhaps at the risk of a higher likelihood of neutropenic infections. Large prospective trials are likely needed to answer this question.

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Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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