Rituximab anti-CD20 monoclonal antibody induces marked but transient reductions of peripheral blood lymphocytes in chronic lymphocytic leukaemia patients

M Ladetto1*, L Bergui1, I Ricca1 S Campana1, A Pileri1 and C Tarella1

1Divisione Universitaria di Ematologia – Azienda Opedaliera S. Giovanni Battista Torino, Italy

Rituximab has been recently proposed as an effective non-chemotherapeutic option for patients with follicle centre lymphoma (FCL). However, less is known on its role in chronic lymphocytic leukaemia (CLL). We thus decided to assess its effectiveness on a panel of 7 patients with refractory or relapsed CLL. Mild (5 patients) or severe (1 patient) adverse reactions were observed during the first hours of Rituximab infusion, almost exclusively at the first course. Symptoms rapidly subsided with temporary drug withdrawal and low dose steroids. All patients could receive the whole scheduled treatment. A striking reduction of peripheral blood (PB) lymphocyte counts was observed in all patients (median 93%; range 57–99%). However, Rituximab was poorly effective towards nodal and splenic disease. Patients required additional treatment after a median time of 70 d (range: 20–180 d). Our data show that Rituximab delivery in CLL patients is feasible and has an acceptable toxicity, although it probably does not represent an ideal treatment option when delivered using schedules originally designed for FCL patients. However, responses observed at PB level suggest that Rituximab has an activity which is not negligible and deserves further investigation in CLL. Future approaches will be directed to the development of alternative schedules which may include dose intensification, combination of Rituximab and chemotherapy, and in vivo purging of peripheral blood progenitor cell harvests for autografting procedures. Medical Oncology (2000) 17, 203–210.

Keywords: chronic lymphocytic leukaemia; Rituximab; monoclonal antibodies

Introduction

The introduction of purine analogues in the treatment of chronic lymphocytic leukaemia (CLL) has represented a major improvement in the management of this neoplasm, and high response rates can now be achieved following treatment with these compounds.1–7 However, since disease relapse is still the rule in CLL, there
Rituximab in chronic lymphocytic leukaemia

I. Ladetto et al.

There is a clear need for innovative treatments for patients with advanced disease. In particular, heavily pretreated patients are not ideal candidates for fludarabine-containing regimens nor for more traditional chemotherapeutic approaches due to increased chemoresistance of tumour cells and high risk for severe infectious episodes. For these patients, drugs other than conventional cytotoxic chemotherapy should be sought.

Unconjugated monoclonal antibodies (moAbs) are a promising therapeutic alternative, allowing effective tumour control in B-cell neoplasms with little or no haematological toxicity. Most recent approaches in this field were based on the development of chimeric or humanised antibodies directed against lineage restricted antigens. Experiences have been made in CLL using the humanised Campath-1H moAb, which is directed against the CD52 antigen, expressed on normal T and B lymphocytes as well as on CLL cells. Preliminary results have shown a marked activity of Campath-1H in CLL patients, with an overall response rate of approximately 50%. However, in past years, a non-negligible toxicity has been associated with Campath-1H therapy and severe, sometimes fatal infectious episodes have been reported, probably due to severe impairment of both humoral and cellular immune response. Although more recent reports have shown that the toxicity of Campath-1H can be greatly reduced by using an appropriate antibiotic prophylaxis, there is still a clear interest in targeting antigens with a more restricted pattern of expression. This might allow us to spare some normal cell populations, such as T lymphocytes, from antibody-induced cytolyis.

The search for a more specific target for moAbs therapy has mainly focused on the CD20 antigen. This molecule displays some attractive properties: like CD52, it lacks shedding from cell membrane; in addition, due to its B-cell lineage restriction, it offers higher specificity compared to the more widely expressed CD52. Promising results have been obtained using the anti-CD20 chimeric antibody Rituximab in patients with CD20-positive indolent lymphomas. In fact, most of these studies focused on follicle centre lymphoma (FCL) where clinical responses have been observed in about 60% of patients with relapsed or refractory disease. However, less is known on the role of Rituximab in other CD20 positive B-cell neoplasms, namely in CLL. Indeed, a few studies performed on a small series of CLL patients have been reported showing only minimal clinical effectiveness of Rituximab. Moreover some authors have observed a high incidence of severe adverse side effects when Rituximab was employed in CLL patients with high lymphocytosis, and the occurrence of fatal events due to tumour lysis syndrome has also been reported. In this study we report our preliminary experience using Rituximab in patients with advanced CLL. Patients were treated with Rituximab since they were not candidates for any cytotoxic treatment due to resistant CLL or concurrent disease. Results in seven patients with relapsed or refractory CLL show that Rituximab can be administered to patients with advanced CLL with mild toxicity. Moreover Rituximab induced marked responses at peripheral blood (PB) level, although nodal and splenic disease appeared unresponsive to this treatment. We thus conclude that Rituximab in CLL has an activity which is not negligible. Its use deserves further investigation, mostly through the development of novel treatment schedules which might include dose intensification, combined therapeutic modalities and in vivo purging of PB progenitor cell harvests for autografting procedures.

Patients and methods

Eligibility and patient characteristics

Adult patients with either refractory or relapsed CLL were considered eligible for the study. Main inclusion criteria were a need for treatment usually due to progressive lymphocytosis together with the impossibility to employ standard chemotherapeutic approaches due to refractory CLL or concurrent disease. An immunophenotype-based diagnosis of CLL and a documented CD20 positivity were required to enter the study. Performance status, platelets and haemoglobin levels, liver and renal functions, presence of chronic infectious disease, bulky tumour, and extension of PB and/or bone marrow involvement were not used as criteria to exclude patients from the study.

Delivery modality

Rituximab, 375 mg/m², was administered intravenously, once weekly, for a total of four infusions.