Adding fresh frozen plasma to rituximab for the treatment of patients with refractory advanced CLL

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Summary

Background: Many patients with chronic lymphocytic leukaemia (CLL) develop progressive, treatment-resistant disease. Rituximab (RTX), a monoclonal antibody targeting CD20 on B lymphocytes and widely used in other indolent B cell neoplasms is less efficacious in CLL, possibly due to associated complement deficiencies.

Objective: To examine in open trial whether providing complement by concurrent administration of fresh frozen plasma (FFP) will enhance the effect of RTX in CLL.

Setting: Outpatient haematology clinics in Israel and Greece.

Patients: Five patients with severe treatment-resistant CLL. All had been previously treated with fludarabine and three also failed treatment with RTX.

Intervention: Two units of FFP followed with RTX 375 mg/m2 as a single agent, repeated every 1–2 weeks, as needed.

Results: A rapid and dramatic clinical and laboratory response was achieved in all patients. Lymphocyte counts dropped markedly followed by shrinkage of lymph nodes and spleen and improvement of the anaemia and thrombocytopenia. This could be maintained over 8 months (median) with additional cycles if necessary. Treatment was well tolerated in all cases.

Conclusion: Adding FFP to RTX may provide a useful therapeutic option in patients with advanced CLL resistant to treatment.

Introduction

Chronic lymphocytic leukaemia (CLL) is characterized by a progressive accumulation of monoclonal B lymphocytes in the bone marrow, lymphatic organs and blood. It is the most common leukaemia in the Western world accounting for about a third of all leukaemias in the USA with about 15 000 newly diagnosed patients every year. CLL is considered to be an indolent disease associated with prolonged survival and death of other causes. However, this is true for about a third of the cases only. Even with the use of newer therapies, relapsed or resistant progressive disease frequently supervenes posing a complex therapeutic challenge.

Rituximab (RTX) is a chimeric IgG1 monoclonal antibody that specifically targets the CD20 surface antigen uniquely present on B lymphocytes. It was first approved for the treatment of low-grade B-cell non-Hodgkin’s lymphoma (NHL), and since then,
much valuable experience has been gained and RTX is now playing an increasingly important role in the treatment of B-cell lymphomas.\textsuperscript{2} Despite the fact that CLL is an indolent B-cell neoplasm and is considered identical to the mature peripheral B-cell small lymphocytic lymphoma, RTX in CLL is less efficacious than in indolent NHL.\textsuperscript{3,4} The lower density of CD20 on B-CLL cells may play a role,\textsuperscript{5} however, the causes of the lesser susceptibility of CLL to RTX remain poorly understood.

Complement deficiencies have been identified in many CLL patients and appear to be more pronounced in patients with more advanced disease and higher Rai stage.\textsuperscript{6,7} Since complement-mediated cell lysis is one of the major mechanisms of RTX action,\textsuperscript{8} we hypothesized that the therapeutic effect of RTX in CLL may be enhanced by the provision of complement through the concurrent administration of fresh frozen plasma (FFP). We report the results of this treatment in the first five patients treated so far.

### Patients and methods

The patients’ characteristics prior to the treatment are presented in Table 1. All were diagnosed 8–18 years before they came to our attention (median 12 years) and had advanced, treatment-refractory CLL (Table 1). All five patients had stage IV disease, according to the Rai staging system. One of the patients showed poor response to RTX used as a single agent and two other patients failed RTX in combination with CHOP-like chemotherapy. All patients had been treated with fludarabine in the past and no sustained effect could be obtained. Thus, despite previous treatments, all patients had marked lymphadenopathy and splenomegaly, peripheral blood lymphocyte counts of $163–448 \times 10^9/L$ and associated significant anaemia and thrombocytopenia (Table 1). Lymph nodes were assessed by clinical examination and spleen size was determined by either clinical examination or ultrasound before treatment and confirmed by ultrasound in all cases following treatment. Patients were enrolled after other treatment options (detailed in Appendix 1) have failed, with the idea that their status before and after treatment might be considered as the control. They were selected according to their clinical status, treatment failure, willingness to sign an informed consent and lack of known contraindications for plasma therapy. Our treatment consisted of two units of FFP followed with standard-dose RTX as a single agent: 375 mg/m\textsuperscript{2} in most cycles, repeated every 1–2 weeks up to a total of 2–5 cycles. All patients gave their informed consent and none had a known contraindication to plasma therapy.

### Results

Toxicity was minimal and the treatment was well-tolerated in all cases. Patient 2, known to be allergic to allopurinol, developed a moderate tumour lysis syndrome which resolved with standard treatment. Disease-related parameters after treatment and survival duration are summarized in Table 2. Peripheral blood lymphocyte counts decreased dramatically and rapidly from a pre-treatment median of $178 \times 10^9/L$ (range $163–448 \times 10^9/L$) to a median of $9.8 \times 10^9/L$ (range $0.9–74.3 \times 10^9/L$). Neutropenia did not occur. Splenomegaly and lymphadenopathy significantly improved as did the anaemia (median haemoglobin 13.0 g/dl vs. 9.7 before treatment) and the thrombocytopenia
associated with advanced disease. A major improvement of clinical signs and symptoms was achieved in all patients. The response was durable (Table 2), excluding patient 1 who was already reported,\(^9\) who died of *Escherichia coli* sepsis 4 months after the last cycle. In that patient too, the CLL showed good partial response that was maintained till her death of septicemia.

### Discussion

We show that a rapid and dramatic clinical and laboratory response to standard-dose RTX can be achieved by adding FFP to RTX. Five CLL patients with advanced disease and very high lymphocyte counts who were refractory to previous treatments responded to this combination in an initial open, non-controlled trial. These patients were heavily pre-treated with alkylating agents, vinca alkaloids, doxorubicin and fludarabine, and patients 1, 3 and 5 had also already been treated with RTX—alone or in combination with chemotherapy (Appendix 1). Nevertheless, their CLL remained poorly controlled, their quality of life was poor and their prognosis was grim. All patients were markedly symptomatic, with combinations of B symptoms, symptoms of severe anaemia and recurrent infections predominating. All these facts (Table 1) made the clinical results obtained by the combined FFP/RTX treatment more noteworthy. The patients’ responses were highly impressive both in their magnitude and in their time frame (Table 2): within days after FFP and RTX were administered, WBC and lymphocyte counts markedly decreased, and later, shrinkage of neoplastic lymphatic tissue in the lymph nodes and spleen was observed and cytopenias significantly improved (particularly the anaemia). These patients have been followed thus far for a median of 8 months (range 4–24 months), during which their response was durable and is already well over a year in two of the patients. Thus, response was durable, and persisted with no additional treatment. Despite these early promising results, a longer follow-up is needed and more patients will have to be studied before the efficacy of this treatment over time can be fully evaluated.

The simplicity, low cost and safety of using adjunctive FFP in RTX-treated CLL patients is an additional asset. The mechanism by which RTX-mediated B-cell depletion in CLL is so markedly enhanced by FFP requires further elucidation. Complement-dependent cytotoxicity and cell lysis (CDC), apoptosis, and antibody-dependent cellular cytotoxicity (ADCC) were suggested as the major mechanisms mediating the cytoreductive effect of RTX.\(^8\,10\) CDC but not ADCC shows marked correlation to the level of expression of CD20.\(^11\) It is possible that providing FFP-derived complement is the factor that initiated the response by correcting qualitative and quantitative abnormalities of the complement system, previously reported in CLL patients with advanced disease.\(^6\,7\) Even normal complement may be rapidly depleted as a consequence of RTX therapy.\(^12\) Thus, supplying complement and enhancing complement-dependent cell lysis by the FFP/RTX combination may be the crucial factor. However, this is not the only mechanism possible. FFP would have provided immunoglobulins which are frequently very low in most patients with CLL and could affect the kinetics of RTX metabolism. These postulates require further study. Nevertheless, even now, the possibility of improving the efficacy of RTX in other conditions in which it is used; especially those associated with complement alterations such as systemic lupus

### Table 2  Patients’ data after FFP/RTX treatment

<table>
<thead>
<tr>
<th>Number of cycles(^*)</th>
<th>B symptoms</th>
<th>Lymph/mL</th>
<th>Hb(gm)/Plt/mL</th>
<th>LN/spleen</th>
<th>Other</th>
<th>Overall survival(^#) (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>–</td>
<td>38 200</td>
<td>11.1/92 000</td>
<td>2 cm/17 cm</td>
<td>Ambulatory, diarrhea resolved</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>900</td>
<td>13.0/128 000</td>
<td>Normal/13 cm</td>
<td>24+</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>3 200</td>
<td>11.0/58 000</td>
<td>3 cm/13 cm</td>
<td>Asymptomatic</td>
<td>15+</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>9 800</td>
<td>14.2/83 000</td>
<td>Normal/Normal</td>
<td>Asymptomatic</td>
<td>4+</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>74 300</td>
<td>14.7/140 000</td>
<td>Normal/14 cm</td>
<td>COPD</td>
<td>8+</td>
</tr>
</tbody>
</table>

\(^*\)Therapy was then stopped and the patient followed.
COPD: chronic obstructive pulmonary disease; LN: lymph nodes; mL: microliter; Hb: haemoglobin; Plt: platelets.
\(^#\) Survival in months since last FFP/RTX cycle.
(-): absence of B symptoms.
erythematous (SLE)—without adding significantly to either cost or toxicity—remains highly intriguing. Meanwhile, when confirmed in larger series of patients and in controlled settings, adding FFP to RTX may provide a useful therapeutic option in patients with advanced CLL resistant to immunotherapy and chemotherapy.

**Conclusion**

Our initial observations in the treatment of five patients with advanced, treatment-resistant CLL suggest that the concurrent administration of plasma with RTX may afford a remarkable clinical response that can be maintained. The clinical and haematological improvement was observed within days and occurred even in three of the patients who had failed standard RTX treatment. The administration of plasma may have corrected complement abnormalities associated either with the CLL or with RTX action and appears to be safe. Further controlled studies are required, but even now, the possibility that RTX action may be enhanced by this simple, cost effective method, should be noted.

**References**


**Appendix 1**

The previous treatment regimens that were tried and failed in each of the patients were as follows:

**Patient 1.** Chlorambucil, CHOP; Fludarabine/Cyclophosphamide; RTX.

**Patient 2.** Chlorambucil, cyclophosphamide, vincristine, prednisone (COP); Fludarabine/Cyclophosphamide.

**Patient 3.** Chlorambucil, COP; Fludarabine; RTX.

**Patient 4.** Fludarabine.

**Patient 5.** Chlorambucil, COP; Fludarabine; RTX.