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Radioimmunotherapy Consolidation using ¹³¹I-Tositumomab for Patients with Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma in First Remission

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Abstract

Despite initial responses to chemoimmunotherapy, relapse and minimal residual disease (MRD) remain major issues in treatment of CLL/SLL patients. We administered ¹³¹I-tositumomab to patients in CR or PR after induction chemotherapy. Toxicities and rate of PR to CR conversion and MRD elimination were assessed three months later. The study stopped prematurely after enrolling 16 patients. Four (25%) were in CR, 12 (75%) in PR, and 12 (75%) had MRD. Three months after treatment with ¹³¹I-tositumomab, CR was achieved (n=8; 50%) or sustained (n=4; 25%) in 12 patients and MRD was eliminated in 4 of 12 patients (33%). Hematologic toxicities were anemia in 1 patient (6%), neutropenia in 13 (81%), and thrombocytopenia in 8 (50%). Two patients (12%) developed MDS 17 and 20 months after consolidation. Consolidation with ¹³¹I-tositumomab for CLL/SLL patients in first remission is feasible and may provide the benefit of converting PR to CR and/or eliminating MRD.

Keywords

CLL; SLL; Consolidation; Radioimmunotherapy; ¹³¹I-Tositumomab; minimal residual disease

Introduction

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in western countries.(1) Chemotherapeutic regimens such as fludarabine and rituximab with (FCR) or without (FR) cyclophosphamide and the combination of bendamustine with rituximab (BR) have shown considerable activity in patients with untreated CLL.(2-4) Although most patients achieve a response, the vast majority of these patients will experience relapse and most patients will have MRD after initial therapy.(5, 6) A growing body of literature has

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suggested the importance of eliminating MRD after initial therapy in regards to the long-term outcomes of CLL patients.(7-9)

Radioimmunotherapy (RIT) using radiolabeled anti-CD20 antibodies was introduced to potentially improve the efficacy of antibody therapy for B-cell lymphomas.(10) Although radiolabeled antibodies have significant efficacy in the treatment of indolent lymphoma, their use in CLL has been limited by the extensive bone marrow involvement and the consequent risk of severe and prolonged myelosuppression. In an earlier study, RIT decreased lymphadenopathy in 4 of 5 pretreated CLL patients but hematologic toxicity and increased infection rates were reported as major limiting factors.(11) In a phase-II study, Jain *et al.*, explored the use of RIT with ⁹⁰Y-ibritumomab tiuxetan for treatment of CLL in the consolidation setting in 14 heavily pre-treated CLL patients.(12) Clinical outcomes were not promising given the low response rate (7%) and high-rate of hematologic toxicity (92%). Lack of success in that study was thought to be, at in least in part, secondary to inclusion of patients with refractory diseases who had previously failed multiple lines of treatment. Accordingly, in this study we investigated the tolerability and efficacy of standard non-myeloablative doses of ¹³¹I-tositumomab following primary induction chemotherapy in CLL and small lymphocytic lymphoma (SLL) patients in first remission, with the goal of increasing the CR rate and minimizing the MRD burden.

Patients and Methods

Eligibility

Patients with CD20-positive, CLL/SLL were eligible if they were over the age of 18 years and if they had received prior therapy and were in first remission with a partial (PR) or complete response (CR) to treatment at the time of enrollment. Prior to the first treatment, patients with CLL must have had either Rai stage III/IV disease or Rai stage I/II with evidence of disease activity as defined by the NCI 1996 guidelines (13) and patients with SLL must have been Stage III or IV per Ann Arbor staging system. Patient were included if they had no more than 25% intra-trabecular marrow space involved by disease in a bone marrow biopsy done within 30 days of receiving the radiolabeled antibody. Patients also required to have a granulocyte count $\geq 1,500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, serum creatinine <2 times upper limit of normal (ULN), total bilirubin <2 times ULN and AST <5 times ULN within 14 days of planned dosimetric infusion. Patients with prior radiolabeled antibody treatment, with active brain or leptomeningeal involvement or with active renal or cardiac failure were excluded. Patients were also excluded if they had prior malignancies (except for non-melanoma skin cancers or *in situ* cervical cancer) unless they were disease-free for 5 years. All patients signed a written informed consent in accordance with institutional and federal guidelines.

Treatment Protocol

Between 90-180 days after achieving a CR or PR, ¹³¹I-tositumomab was administered in two discrete steps. First, a dosimetric dose of ¹³¹I-tositumomab was given on day 0 and consisted of a 1-hour infusion of 450 mg of unlabeled tositumomab followed by a 20-minute infusion of 5 mCi (35 mg) of ¹³¹I-tositumomab. Total-body gamma counts using a gamma

camera were obtained on three occasions over the next week (day 0; day 2, 3, or 4; and on day 6 or 7). Using these counts, calculations based on standard internal radiation dosimetry methods were performed to determine the patient-specific activity (in millicuries) of radiolabeled tositumomab required to deliver a maximum tolerated therapeutic dose of 75 cGy total-body dose (65 cGy in patients with a platelet count $\geq 100,000$ and $<150,000$ cells/mm³). For patients weighing more than 137% of their lean body weight the calculations to determine the ¹³¹I-tositumomab antibody activity were performed using an upper limit of mass (maximum effective mass) based upon height and gender. Second, the therapeutic dose was administered between day 7 and day 14. A 450 mg unlabeled tositumomab dose was administered, followed by the patient-specific (in millicuries) activity labeled to 35 mg of tositumomab. Thyroid protective agents were initiated at least 24 hours prior to administration of the ¹³¹I-tositumomab dosimetric dose and continued until 2 weeks after administration of the therapeutic dose.

Assessment of Clinical Responses

Three months after the treatment dose, efficacy and response were recorded per NCI working group guidelines (13) and toxicity assessments were recorded based on the CTCAEv3.0. MRD was assessed by eight-color flow cytometry with a detection limit of 10^{-3} to 10^{-4} on bone marrow samples to detect CLL/SLL cells.(14) Any level of residual disease by flow cytometry or cytogenetics (CG) was considered MRD positive and negativity of both test was required to classify a patient as MRD negative. Rituximab levels were determined using a standard ELISA method with a monoclonal anti-rituximab idiotype antibody before administration of ¹³¹I-tositumomab as previously described.(15)

Statistical Considerations

This study was planned to enroll 30 patients and to proceed to a larger phase II trial if the observed 2-year progression-free survival (PFS) among the patients who received ¹³¹I-tositumomab was 70% or higher. However, the study stopped after enrolling 16 patients because of slow accrual as well as manufacturer's decision to stop production of the drug. Mann–Whitney–Wilcoxon was used to compare the rituximab level medians between different treatment response groups.

Results

Between 2008-2012, 16 patients (CLL=11, SLL=5) received consolidative ¹³¹I-tositumomab in first CR or PR. The patients' baseline characteristics are summarized in Table 1. The median age was 61 (range, 38-78). Seven patients (44%) had high-risk disease based on cytogenetics or molecular profile. Two patients (13%) had 11q22 deletion and one had mutated TP53 (6%). Increased CD38 ($>30\%$) and ZAP-70 ($>20\%$) expression were present in 3 of 11 and 6 of 7 patients who were tested, respectively, and unmutated IgVH was detected in 1 of 3 tested patients. At the time of consolidation, 4 (25%) patients were in CR and 12 (75%) were in a PR after their upfront chemoimmunotherapy regimen. There was evidence of MRD at the time of consolidation in 12 patients (75%) assessed by MFC. Median time interval from day one of their last chemotherapy to ¹³¹I-tositumomab

consolidation was 15.4 weeks and ranged from 10 to 29 weeks. Dose reduction was needed in 7 patients (44%) based on cytopenia (n=4) or pre-treatment weight (n=3).

Three months after consolidation with ^{131}I -tositumomab, 12 patients were in CR (80%). This included 4 patients (33%) who sustained the CR in addition to 8 patients (66%) who were in PR at the time of consolidation but achieved CR after consolidation. Other outcomes consisted of PR in 1 patient, nodular PR in 1, and disease progression in 1 patient. One patient was lost to the follow-up. Among patients who were in PR after consolidation, there was improvement in lymphadenopathy in 5 of 6 of patients with measureable disease prior to ^{131}I -tositumomab. Likewise, ^{131}I -tositumomab eliminated MRD in 4 of 12 patients (33%) with a negative CG or MFC assay at 3 months. (Fig. 1)

Overall, the median pre-consolidation rituximab level was 6.9 $\mu\text{g/ml}$ (range, 0.3-30.6). Patients with CR at 3 months had significantly higher median levels of pre-treatment rituximab levels (11.0 vs. 2.32 $\mu\text{g/ml}$; $p = 0.02$). Patients who were in PR before consolidation and achieved CR after ^{131}I -tositumomab had higher median rituximab levels compared to the ones who did not achieve CR (11.7 vs. 2.3 $\mu\text{g/ml}$; $p=0.04$). However, there was no difference between the pre-consolidation rituximab levels of patients who were MRD positive before consolidation and became negative after treatment and those who remained MRD positive (8.2 vs. 7.2 $\mu\text{g/ml}$; $p=0.8$).

Hematologic toxicities over the first 3 months post therapy were grade 3 anemia in 1 patient (6%), grade 3 or 4 neutropenia in 13 (81%), and grade 3 or 4 thrombocytopenia in 8 (50%). One patient (6%) had evidence of hypogammaglobulinemia (IgG <400 mg/dL) 3 months after the consolidation. Six patients (37%) required blood or platelet transfusions. Two patients (12%) needed myeloid growth factor support. One patient was hospitalized within 3 months of RIT for neutropenia-related sepsis/typhlitis. Secondary malignancies were observed in 5 patients (31%) and included myelodysplastic syndrome (MDS) (n=2; 12%), basal cell carcinoma (n=2; 12%) and squamous cell carcinoma of skin (n=1; 6%). MDS was diagnosed in the 2 patients 17 and 20 months after RIT, respectively. These 2 patient received FR (6 cycles) and FCR (6 cycles) before the consolidative RIT, respectively, yet none of these patients received any other cytotoxic chemotherapy other than the fludarabine-based treatment and RIT before the MDS diagnosis and none had any evidence of dysplasia at the time of CLL diagnosis.

At a median follow-up of 48 months, three patients (19%) died, one from complications of MDS, one from multi-organ failure secondary to disease progression and one from sepsis while in remission. Seven patients (44%) had relapse during the follow-up. The median duration of overall survival was not reached and the median PFS was 42 months. (Fig. 2)

Discussion

The current standard of care for front-line treatment of CLL/SLL employs use of cytotoxic chemotherapy with fludarabine-based regimens being the most commonly used treatments in this setting.(16) While majority of patients achieve an initial CR or PR, presence of MRD after treatment and later relapses remain major issues.(5, 6) Assessment of MRD status after

CLL treatment and its association with clinical outcomes have been an active area of investigation.(7, 9, 17) For example, the importance of a negative MRD status upon completion of the initial chemotherapy for CLL was recently demonstrated by Strati *et al.* in 237 patients.(8) In their study, the negative MRD status was found to be independently associated with improvements in both PFS and overall survival. Interestingly, the MRD negative status was associated with a better PFS regardless of the number of treatments delivered. The authors concluded that early MRD eradication may be a reasonable goal of treatment for CLL patients and may even prompt treatment discontinuation. Implementation of novel therapeutic approaches in order to consolidate the response and to increase the number of patients with MRD negative status after the initial treatment may therefore improve clinical outcomes.(8)

In the current study, we demonstrated the feasibility of RIT using ^{131}I -tositumomab for consolidation after first-line chemotherapy for CLL/SLL patients and observed that this approach may be effective in eliminating MRD using an eight-color flow cytometry developed University of Washington (UW)/ Fred Hutchinson Cancer Research Center (FHCRC). (14) RIT consolidation improved the complete clinical response rate from 25% to 80% and eliminated MRD in a third of patients who had evidence of CLL detected by MFC or CG at the end of initial chemotherapy. Although not investigated adequately in CLL to date, several clinical studies have shown the promise of radiolabeled antibodies for treatment of indolent non-Hodgkin lymphoma (NHL). For example, conversion of PR to CR and prolonged relapse-free survival was reported with RIT after induction therapy for advanced stage follicular lymphoma.(18) RIT had previously been studied in the MRD setting in SLL patients. Kaminski *et al.* reported the outcomes of SLL patients who had been enrolled in 4 different clinical trials of ^{131}I tositumomab for NHL.(19) Sixty-four percent (9 of 14) of patients showed a clinical response (PR conversion to CR) and severe neutropenia and severe thrombocytopenia were observed in 14% and 7% of patients, respectively. In the allogeneic transplant setting, our group has previously reported an improved progression-free survival for patients with persistent CLL/SLL and other indolent non-Hodgkin's lymphomas when ^{90}Y -ibritumomab tiuxetan was administered before conditioning regimen (fludarabine and low dose total-body irradiation).(20) In a phase-II study from the M.D. Anderson Cancer Center, Jain *et al.* investigated the effect of consolidation with ^{90}Y -ibritumomab tiuxetan in 14 previously treated CLL patients who were in CR or PR.(12) While conversion of PR to CR was reported in one patient, there was still evidence of MRD at the time of follow-up. Furthermore, most of patients (92%) developed grade 3 or 4 bone marrow toxicity in form of cytopenias. Overall, it was concluded that the rate of hematologic toxicity was likely unacceptable in relapsed patients. It may, however, be argued that the observed profound bone marrow toxicity in that study compared to studies that used RIT for treatment of relapsed NHL patients could be attributed to three factors. First, the CLL patients in the MD Anderson study were heavily pretreated with a median of 5 treatments prior to consolidation with RIT. In our study, patients had only received 1 line of cytotoxic chemotherapy before consolidation with ^{131}I -tositumomab, which may explain the slightly lower rate of hematologic toxicity at 3 months. In our study, the hematologic toxicity profile was largely as anticipated at 3 months with neutropenia being the major cytopenia affecting 81% of the patients. Second, in contrast to the other types of NHL, the

majority of CLL patients have a higher degree of bone marrow involvement, which is a known risk factor for hematologic toxicities in NHL patients undergoing RIT. Although a cut-off of 25% marrow involvement was selected as the inclusion criteria for both studies, higher rates of hematopoietic toxicities in CLL patients may at least in part be attributed to the marrow involvement in these patients. Third, CD20 blockage as a result of prior rituximab treatment and subsequent non-specific marrow toxicity from the unbound circulating radioisotope may also explain the marrow toxicity to some degree.

In our study, two patients (12%) were diagnosed with therapy-related MDS/AML (t-MDS) approximately 1.5 years after completion of treatment. Development of t-MDS has been a potential long-term adverse effect of RIT. In one report, 19 of 746 patients (2.5%) who received RIT with ⁹⁰Y-ibritumomab tiuxetan for treatment of NHL were diagnosed with t-MDS or acute myeloid leukemia (AML) at a median of 1.9 years (range, 0.4-6.3) after treatment with RIT.(21) Also, Bennett *et al.* followed 985 patients after treatment with ¹³¹I-tositumomab for NHL and reported a confirmed diagnosis of t-MDS/AML in 23 patients (2.3%). All those patients had previously received other cytotoxic treatments and in fact no t-MDS/AML was reported in patients who received RIT as the initial treatment.(22) Secondary myeloid malignancies have also been reported after FCR-based treatments. Benjamini et al. followed 234 patients after treatment with FCR-based treatments for CLL and reported a t-MDS/AML rate of 5.1%. The median time to development of secondary myeloid malignancy was 2.7 years (range, 1.1-7.8) in their cohort. (23). Realizing the small sample size in our study, the shorter time interval between the treatment and development of myeloid malignancy in 2 patients appears to be related the prior fludarabine exposure in combination with RIT.

We examined the correlation between pre-consolidation plasma rituximab levels and the clinical outcomes. Patients with a PR to the initial treatment who achieved a CR after consolidation with ¹³¹I-tositumomab had a median rituximab level of 11.7 µg/ml that was significantly higher than the corresponding level of 2.3 µg/ml in patients who did not achieve CR after consolidation (p=0.04). The results should be interpreted with caution considering the small sample size. However, given the known dose-effect relationship between rituximab and clinical outcomes in CLL, it is possible that an ongoing effect of rituximab in patients with higher plasma levels augmented the response to RIT and led to the observed improvement in the clinical outcomes (PR conversion to CR).(24) It is unclear why such a difference was not observed when conversion of MRD positive disease to MRD negative status was chosen as the clinical outcome of interest, although the possibility of low statistical power to detect such an association cannot be ruled out.

Our study had limitations. First, lack of a control arm makes the interpretation of efficacy and toxicity data challenging especially because the historical data was based on studies that were significantly different from ours in terms of design, sample size and the study settings. Second, interpretation of feasibility of a non-randomized study was limited and can only be applied to the patients who actually received the RIT and not to the ones who were intended to be treated. It remains unclear that what percentage of patients can practically receive RIT consolidation after finishing the frontline chemoimmunotherapy. Third, the small sample size made the statistical analyses less reliable especially for sub-groups.

Nonetheless, while further long-term follow-up studies are needed to assess the possible long-term side effects as well as the clinical effectiveness of this approach, consolidation RIT with ^{131}I -tositumomab after first remission appears to be feasible and may provide the potential benefit of converting PR to CR or especially eliminating MRD in CLL/SLL patients.

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Figure 1.

Clinical response to RIT. Comparing the frequency of CR and PR (panel A) and MRD negativity (panel B) before (left bar) and after (right bar) treatment with ^{131}I -Tositumomab. RIT: radioimmunotherapy; CR: complete response; PR: partial response; nPR: nodular partial response.

* One patient was lost to follow-up.

Figure 2.

Progression-free (panel A) and overall (panel B) survival of all patients (n=16). At the time of analysis, the median duration of PFS was 40 months and median duration of the OS had not been reached.

Table 1
Patient Characteristics (n=16)

Mean age, years (range)	61 (38-78)
Female sex, n (%)	5 (31%)
Diagnosis, n (%)	
CLL	11 (69%)
SLL	5 (31%)
Cytogenetics/Molecular characteristics, n (%)	
del 11 q22	2 (12.5%)
TP53 mutation	1 (6.25%)
High CD38 expression (>30%)	3 of 11 (27.2%)
High ZAP-70 (>20%)	6 of 7 (85.7%)
Unmutated IgVH	1 of 3 (33.3%)
Prior Chemotherapy, n (%)	
FR	9 (62.5%)
FCR	4 (25%)
BR	2 (12.5%)
R-CHOP	1 (6.2%)
Disease status before ¹³¹ I tositumomab, n (%)	
CR	4 (25%)
PR	12 (75%)
MRD status before ¹³¹ I tositumomab, n (%)	
Positive	12 (75%)
Negative	4 (25%)
Time from the first day of the last treatment weeks, (range)	15.4 (10-29)

FR: fludarabine, rituximab ; FCR: fludarabine, cyclophosphamide, rituximab; BR: bendamustine, rituximab ; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone