Original Study

Consolidative Radioimmunotherapy After Chemoimmunotherapy in Patients With Histologic Transformation of Indolent Non-Hodgkin Lymphoma

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Abstract

Radioimmunotherapy (RIT) has demonstrated efficacy in histologic transformation (HT) and can be used safely as consolidation after chemoimmunotherapy. We examined our experience using RIT consolidation for HT in 21 patients ineligible for more aggressive therapies, and we described prolonged overall and progression-free survival. The survival outcomes compare favorably to historical data, and the approach has acceptable toxicity in a frail patient population.

Introduction: Histologic transformation (HT) of indolent non-Hodgkin lymphomas is an event that results in considerable morbidity and mortality. The introduction of chemoimmunotherapy regimens has resulted in an improvement in the management of this disease, and consolidation of responses with autologous stem cell transplantation appears efficacious. Many patients are not eligible for high-dose therapy, however. Radioimmunotherapy (RIT) has demonstrated single-agent efficacy in HT and can be used safely as consolidation after chemoimmunotherapy. For these reasons, RIT consolidation after chemoimmunotherapy induction has been our standard treatment approach at the University of Rochester for patients with HT who were ineligible for autologous stem cell transplantation. **Patients and Methods:** A retrospective cohort study was performed to describe the clinical outcomes of these patients. Twenty-one patients were identified who received RIT consolidation. The Kaplan-Meier method was used to estimate the distributions of overall survival and progression-free survival. Comparisons were made between patients with pathologic HT and the combination of clinical HT and composite lymphoma using the log-rank test to compare survival curves. **Results:** The median overall survival of the cohort was 84 months, and progression-free survival was 38 months. The major toxicity was myelosuppression, and 2 deaths were attributed to therapy. One case of therapy-related acute myeloid leukemia was noted. **Conclusion:** In a population of patients ineligible for high-dose therapy with autologous stem cell support, consolidation of response to chemoimmunotherapy with RIT was well tolerated and should be considered in patients with disease responsive to induction therapy.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. 6, 322-8
Keywords: ^{131}I-tositumomab, ^{90}Y-ibritumomab tiuxetan, indolent lymphoma, radioimmunoconjugate, transformed lymphoma

Introduction

Histologic transformation (HT) of follicular lymphoma (FL) and other indolent non-Hodgkin lymphomas (NHL) represents a change in the natural history of disease in patients, and leads to significant morbidity and mortality. HT has been particularly well characterized in FL and occurs at a rate of 2% to 3% per year.[1-4] Historically, HT has carried an abysmal prognosis, with a median overall survival (OS) ranging from 1.2 to 1.8 years.[3,4] While a more contemporary series in the rituximab era demonstrates an improvement in OS, HT continues to represent a challenge in patients, especially those who may not tolerate aggressive therapy.[1]

Given the historically poor prognosis of HT, consolidation with autologous stem cell transplantation (ASCT) has been pursued in patients eligible for this approach. There are data from multiple

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Submitted: Mar 19, 2016; Accepted: Mar 27, 2016; Epub: Apr 2, 2016

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2016.03.014

retrospective series to support the use of ASCT as consolidation.[5-12] Many patients cannot benefit from this consolidative approach, as not all patients are eligible because of age and comorbidities. Effective management of this vulnerable patient population represents an unmet need in the field. The optimal management of these patients is unclear, as conducting large prospective trials has proven difficult.

Radioimmunotherapy (RIT) has shown activity as a single-agent in heavily pretreated patients with HT. In a multicenter phase 2 study of single-agent ^{131}I-tositumomab, 10 patients with HT experienced an objective response rate (ORR) of 60%, with the majority experiencing a complete response. Additionally, durability was demonstrated, with a median duration of response of 12 months.[13] In the pivotal study for ^{131}I-tositumomab, a lower but still clinically significant ORR of 39% was observed in patients with HT. Nearly half of these patients had bulky disease and had received a median of 4 prior therapies.[14] In a study of ^{90}Y-ibritumomab tiuxetan versus rituximab monotherapy, an ORR of 56% was seen in patients with HT treated with ^{90}Y-ibritumomab tiuxetan, but this was not superior to rituximab monotherapy.[15] The responses have been durable in a subset of patients with B-cell NHLs treated with RIT. Integrated analysis of 250 patients from several clinical trials with ^{131}I-tositumomab identified 81 patients who had a time to progression of $>$ 12 months and who were classified as experiencing a durable response. Of these patients with durable response, 23% had HT.[16]

Consolidation with RIT after induction chemotherapy is a safe and effective strategy in FL. These studies include the Fludarabine, Mitoxantrone, Zevalin (FLUMIZ) study and the randomized First Line Indolent Trial (FIT) study, in which consolidation with ^{131}I-tositumomab was superior to induction with chemotherapy alone.[17,18] Additionally, S0016, which randomized patients to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or CHOP with ^{131}I-tositumomab, demonstrated similar excellent outcomes in regard to progression-free survival (PFS) and OS in both arms.[19] Consolidation with RIT after CHOP or R-CHOP induction has also been studied in higher-grade lymphomas such as diffuse large B-cell lymphoma (DLBCL); however, there are no randomized data to support the use of RIT for consolidation in DLBCL.[20,21]

On the basis of the safety demonstrated with RIT consolidation after chemoimmunotherapy in FL and DLBCL, the poor outcomes in HT, and the single-agent activity of RIT in transformed histology, our approach to HT in patients deemed unfit for ASCT has been treatment with R-CHOP or an alternative as induction therapy, followed by RIT consolidation with either ^{90}Y-ibritumomab tiuxetan or I^{131} tositumomab. This approach has not previously been reported in the literature. We thus conducted a retrospective cohort study to describe the clinical outcomes of patients treated in this manner. We report the results of this strategy in 21 consecutive ASCT-ineligible patients with HT.

Patients and Methods

Clinical records from the nuclear medicine department at the University of Rochester Medical Center were queried to identify consecutive patients $>$ 18 years old who had received RIT from January 1, 2004, to August 1, 2013. The chart of each individual patient was reviewed by an investigator (P.M.R.) to determine inclusion. Eligibility for inclusion was confirmed by a second investigator (J.W.F.). Inclusion criteria were as follows: (1) clinical, composite, or pathologic diagnosis of HT, and (2) receipt of RIT after response to rituximab and chemotherapy. Patients who had received RIT as a single-agent therapy were excluded from this analysis.

Pathologic HT was defined as biopsy-confirmed DLBCL or Burkitt-like lymphoma by the World Health Organization classification $\geq$ 6 months after a biopsy was performed establishing indolent lymphoma diagnosis (pathologic HT), or after clinical evidence of transformation as defined in previous cohorts[1,3] in the absence of biopsy confirmation (clinical HT). Composite diagnosis of HT was defined as concurrent indolent and large-cell lymphoma. All pathology was reviewed in the department of hematopathology at the University of Rochester Medical Center.

The primary end point was OS. PFS was a secondary outcome. OS was defined as the time from HT until death or last follow-up. PFS was defined as the time from HT until progression or death from any cause. Follow-up was determined from the time of HT until death or last follow-up.

Statistical Analysis

The Kaplan-Meier method was used to estimate the distributions of OS and PFS. Comparisons were made between patients with pathologic HT and the combination of clinical HT and composite lymphoma using the log-rank test to compare survival curves. Comparisons were also made between patients who had received rituximab before transformation and those who had not received rituximab. Hypothesis tests were conducted at the .05 level of significance, and all *P* values and confidence intervals were 2 sided. All analyses were performed by SAS 9.2 software (SAS Institute, Cary, NC, USA).

Results

Clinical Characteristics

A total of 21 patients were identified who met the inclusion criteria. Table 1 summarizes the clinical characteristics and demographics of the study population. The median age of patients included in the analysis was 66 years (range, 44-90 years). There was a slight male predominance. FL was the most common indolent lymphoma that preceded HT. Patients had received a median of 1 treatment before HT. Thirteen patients received rituximab before HT. More detailed information relating to treatments is included in Supplemental Table 1 in the online version. Eleven patients were classified as having pathologic HT, 7 with a clinical diagnosis of HT and 3 patients with composite lymphoma at diagnosis. Nine patients received ^{131}I-tositumomab and 12 received ^{90}Y-ibritumomab tiuxetan. Ten patients were determined to be ineligible for ASCT due to frailty and age, 6 patients refused consolidation with ASCT, 3 patients were not able to mobilize stem cells or previously had an ASCT, and 2 patients had cardiomyopathy, which prohibited ASCT.

Treatments at Time of HT

The majority of patients (17/21) received R-CHOP at the time of HT. Of the remaining patients, one patient each received