A phase 2 trial of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab for previously untreated follicular non-Hodgkin lymphoma: Southwest Oncology Group Protocol S9911

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Advanced follicular lymphoma is incurable with conventional chemotherapy and radiotherapy. The Southwest Oncology Group (SWOG) conducted a phase 2 trial (S9911) of a novel regimen consisting of 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy followed 4 to 8 weeks later by tositumomab/iodine I 131 tositumomab (anti-CD20 antibody) in 90 eligible patients with previously untreated, advanced stage follicular lymphoma. Treatment was well tolerated. Reversible myelosuppression was the main adverse event and was more severe during CHOP chemotherapy than following radioimmunotherapy. The overall response rate to the entire treatment regimen was 90%, including 67% complete remissions (CRs plus unconfirmed CRs [CRu's]) and 23% partial remissions (PRs). Twenty-seven (57%) of the 47 fully evaluable patients who achieved less than a CR with CHOP improved their remission status after tositumomab/iodine I 131 tositumomab. With a median follow-up of 2.3 years, the 2-year progression-free survival (PFS) was estimated to be 81%, with a 2-year overall survival of 97%. This study has established the feasibility, tolerability, and efficacy of this regimen for patients with advanced follicular lymphoma. This novel treatment appears promising compared with the SWOG's historical experience using CHOP alone and is currently being compared with CHOP plus rituximab in a randomized phase 3 trial (S0016). (Blood. 2003;102: 1606-1612)

Introduction

Follicular non-Hodgkin lymphoma (NHL) afflicts approximately 15 000 Americans annually and typically pursues an indolent, but inexorable clinical course leading to death a median of 10 years after diagnosis.[1,2] Ten percent to 15% of follicular lymphoma patients present with localized, stage I or II disease, and the use of involved field radiotherapy confers prolonged disease-free survival for 40% to 50% of patients in this small subset.[3] In contrast, there is no evidence that any conventional chemotherapy or radiotherapy approach is curative for the 85% of follicular lymphoma patients who present with disseminated stage III or IV disease, and there is no consensus on the best treatment approach for these patients.[4] Many asymptomatic cases are followed with "watchful waiting," because conventional chemotherapy regimens have not convincingly shown improved survival compared with a policy of expectant therapy.[2] Symptomatic patients are commonly treated with chemotherapy regimens containing alkylating agents (eg, chlorambucil or CVP [cyclophosphamide, vincristine, and prednisone]), or with fludarabine, but randomized studies have not demonstrated a survival advantage for patients treated with these approaches. Because of the curative potential of anthracycline-based regimens for aggressive non-Hodgkin lymphomas, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was tested in 415 indolent lymphoma patients on Southwest Oncology Group protocols.[5] Approximately 90% of these patients achieved objective responses, including 61 (78%) with complete remissions; however, there was no plateau on the survival curves, indicating that by itself CHOP has little curative potential for indolent lymphoma.

High-dose chemoradiotherapy with autologous or allogeneic bone marrow or peripheral blood stem cell transplantation has been attempted with curative intent for treatment of patients with newly diagnosed[6] and relapsed follicular lymphoma.[7] However, the curability of follicular lymphomas with stem cell transplantation and the advisability of performing this procedure remain controversial.

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Most recent attempts to improve the outcome of patients with follicular lymphoma have investigated the utility of adjuvant immunotherapy. Alpha interferon has been tested in combination with chemotherapy in at least 10 randomized clinical trials of indolent NHL, with conflicting conclusions,[8] and its use is uncommon in the United States. Rituximab was combined with CHOP in two phase 2 studies of follicular lymphoma with promising results, raising hopes that anti-CD20–based immunotherapy may synergize with chemotherapy and improve the outcome of patients with this disease.[9-11] Czuczman et al[9,10] treated 40 patients with concurrent rituximab and CHOP, achieving objective remissions in 95% of patients, including 55% complete remissions. No unexpected toxicity was observed with the combination, and the median time to progression was not reached after 50 months of follow-up. Maloney et al[11] treated 85 evaluable patients with 6 cycles of CHOP followed by 4 doses of rituximab and attained an overall response rate of 72%, with 54% complete remissions and a 2-year progression-free survival rate of 74%.

In an effort to augment the efficacy of anti-CD20 monoclonal antibodies, several investigators have explored the feasibility of administering iodine-131– and yttrium-90–radiolabeled antibodies to patients with indolent lymphomas.[12-17] These studies have shown that 50% to 80% of patients with relapsed or refractory follicular lymphomas obtain objective remissions, including 25% to 35% complete remissions. Treatment of newly diagnosed patients with indolent lymphoma is even more effective, with 95% of patients achieving an objective remission with tositumomab/iodine I 131 iodine-tositumomab (Bexxar; Corixa, Seattle, WA), including 74% complete remissions.[18,19] A recent randomized trial demonstrated that yttrium-90 ibritumomab tiuxetan was more effective than rituximab as documented by production of higher overall and complete response rates in patients with relapsed indolent lymphomas.[20]

In view of these findings, the Southwest Oncology Group decided to investigate the efficacy and safety of a novel new approach combining induction chemotherapy with CHOP followed by consolidation with tositumomab/iodine I 131 tositumomab in a phase 2 trial (S9911) for patients with previously untreated advanced follicular lymphoma. This manuscript reports the findings of this phase 2 trial.

Patients and methods

Patient eligibility

Patients older than the age of 18 years with biopsy-proven, untreated, bidimensionally measurable bulky stage II, stage III, or stage IV follicular non-Hodgkin lymphoma (grade I, II, or III) expressing the CD20 antigen were eligible for this trial if they had a Southwest Oncology Group (SWOG) performance status of 0 to 2, a pretreatment granulocyte cell count of 1500/μL or greater, and a platelet count of 100 000/μL or greater. Stage II patients were considered to have bulky adenopathy if they had a mass larger than 10 cm in diameter or a mediastinal lesion greater than one third the thoracic diameter. Patients were excluded if they had received prior chemotherapy, radiotherapy, or immunotherapy; if they were HIV positive; if they had central nervous system involvement, had circulating lymphoid cells exceeding 5000/μL, were pregnant or lactating; or if they had coexistent serious cardiac disease or a prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient had been disease free for 5 years. All patients were notified of the investigational nature of this study and signed a written informed consent approved in accordance with institutional and federal guidelines, including the Declaration of Helsinki. The study was approved by the institutional review boards of the participating institutions.

Pathology review

All diagnostic biopsies were centrally reviewed by expert pathologists of the Southwest Oncology Group to confirm the diagnosis of follicular lymphoma. Excisional biopsies or core needle biopsies large enough to show the follicular architecture were mandatory. Bone marrow biopsies and needle aspirates were insufficient for study entry. CD20 antigen expression was required, as demonstrated by either flow cytometry or immunoperoxidase staining of paraffin sections using anti-CD20 antibodies.

Baseline studies

All patients entered onto this trial were required to undergo a full history, physical examination, complete blood cell count with leukocyte differential, platelet count, chest radiograph or computed tomography (CT) scan, abdominal and pelvic computed tomography, and bone marrow aspiration and biopsy. According to good medical practice, patients were also tested for blood chemistries (including creatinine, liver function tests, uric acid, and lactate dehydrogenase) and thyroid-stimulating hormone (TSH) levels and underwent urinalysis and electrocardiography. Patients with a history of impaired cardiac status were assessed with a cardiac gated blood pool scan (multigated [MUGA] scan) or echocardiography and were eligible only if the cardiac ejection fraction was normal.

Chemotherapy

Patients were treated with standard CHOP chemotherapy every 21 days for 6 cycles. Dosages of 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 (maximum, 2.0 mg) vincristine were administered intravenously on day 1, and 100 mg prednisone was given orally daily for 5 days each cycle. Allopurinol (300 mg orally) was recommended as adjunctive therapy for patients with bulky disease. If there were fewer than 1500/μL granulocytes or fewer than 100 000/μL platelets by the time the next cycle was due, treatment was delayed 1 week and counts were repeated. If, after 2 weeks, counts had not recovered, the patient was treated at 75% of the last dose of cyclophosphamide and doxorubicin received. If grade 3 or 4 infection (according to the National Cancer Institute [NCI] Common Toxicity Criteria) occurred in the setting of chemotherapy-related neutropenia, the doses of cyclophosphamide and doxorubicin were reduced to 75% of the last dose received. Re-escalation was at the discretion of the treating physician. Filgrastim and sargramostim were not administered to prevent neutropenia, but patients who experienced grade 3 or 4 neutropenia or developed neutropenic fever between cycles of chemotherapy could receive growth factors for subsequent cycles of therapy at the discretion of the treating physician. If the bilirubin level rose to 2 to 5 times the institutional upper limit of normal, the doxorubicin and vincristine doses were reduced by 50%, and, if the bilirubin level rose to more than 5 times normal, doxorubicin and vincristine were not administered for that cycle. If the creatinine level rose higher than 2 times the institutional upper limit of normal, the dose of cyclophosphamide was reduced by 25%. Cyclophosphamide was discontinued and the patient was removed from protocol treatment if grade 3 or 4 hemorrhagic cystitis occurred.

Restaging

Patients were restaged 4 to 8 weeks after completion of the sixth cycle of CHOP chemotherapy with physical examination, blood testing, chest radiography or computed tomography, abdominal and pelvic computed tomography, and bone marrow aspiration and biopsies. Patients achieving at least an unconfirmed partial response after 6 cycles of CHOP chemotherapy[21] were eligible for consolidation with tositumomab/iodine I 131 tositumomab provided the granulocyte count was greater than 1500/μL, the platelet count exceeded 100 000/μL, and the bone marrow examination at the completion of CHOP chemotherapy demonstrated no more than 25%

involvement with lymphoma. A second registration was required within 7 days of the last restaging test, and radioimmunotherapy was required to begin within 14 days after the second registration.

Tositumomab/iodine I 131 tositumomab

Eligible patients were treated with radioimmunotherapy as described by Kaminski et al.[12,13] Thyroid glands were protected from radioiodine by administration of either a saturated solution of potassium iodide (SSKI; 4 drops orally 3 times a day), Lugol solution (20 drops orally 3 times a day), or potassium iodide tablets (130 mg orally daily) starting at least 24 hours prior to the dosimetric infusion of the iodine I 131 tositumomab antibody and continuing for 14 days following the therapeutic infusion of iodine I 131 tositumomab. Patients received 2 infusions of radiolabeled antibody, 1 for dosimetry and 1 for therapy. Patients were premedicated with 650 mg acetaminophen orally and 50 mg diphenhydramine orally; then 450 mg unlabeled tositumomab antibody was infused intravenously over 60 minutes followed by iodine I 131 tositumomab (5 mCi [185 MBq] ^{131}I on 35 mg antibody) administered over 20 minutes through an inline 0.22-micron filter. Whole-body anterior gamma camera images were obtained within 1 hour after the completion of the administration of the dosimetric dose on day 1, and then on either day 3, 4, or 5, and again on either day 7 or 8 by means of a gamma camera with a medium- or high-energy collimator. The counts described in "Chemotherapy" were used to calculate the activity to be administered to deliver 75 cGy according to a standard nomogram (unless these were adjusted for obesity and/or platelet count). For obese patients, the dose was adjusted to 137% of their calculated lean body mass. The administered activity (millicuries [megabecquerels] of iodine I 131 tositumomab) for patients with platelet counts of 100 000 to 149 999/mm^3 was adjusted to deliver 65 cGy. The therapeutic infusion of tositumomab/iodine I 131 tositumomab was administered 7 to 14 days after the dosimetric infusion of antibody. Patients were again premedicated with acetaminophen and diphenhydramine before receiving infusions of 450 mg unlabeled tositumomab antibody intravenously over 60 minutes and then 35 mg iodine I 131 tositumomab labeled with an amount of ^{131}I calculated to deliver a 75-cGy whole-body dose over 20 minutes (65 cGy if the platelet count was 100 000 to 149 999/μL). Tositumomab/iodine I 131 tositumomab was administered a mean of 54 days after the last dose of CHOP (range, 16-86 days: standard deviation, 13 days). Tositumomab/iodine I 131 tositumomab administration was permitted either on an outpatient basis or with inpatient isolation, depending on state radiation safety regulations. Patients treated as outpatients were given guidelines to avoid contact with children or pregnant women, to sleep in separate beds, to avoid public transportation, to use separate eating utensils, and to use separate bathrooms for 1 to 2 weeks after treatment.

Assessment of response

Patients were centrally reviewed for response (partial remission [PR], unconfirmed complete remission [CRu], or CR) according to the criteria of an international workshop.[21] Response assessments were performed at 8 weeks, 6 months, and 12 months after completion of iodine I 131 tositumomab therapy and annually thereafter, and were based on performance of a medical history, physical examination, complete blood cell count with leukocyte differential, platelet count, chest radiograph or CT scan, abdominal and pelvic computed tomography, and bone marrow aspiration and biopsy. The same radiographic technique was required for baseline and follow-up response assessments. Patients were removed from protocol treatment if they experienced progression of disease or unacceptable toxicity or if they declined protocol therapy. Human antimouse antibody testing was not performed in this study.

Statistical considerations

This study was based on estimation. Eighty evaluable patients were sufficient to estimate the 2-year progression-free survival rate (given complete follow-up) to within 11% (95% confidence interval). (Previous SWOG studies have shown approximately 65% 2-year progression-free survival in this patient group. This design gives 86% power to detect a 15% difference in 2-year progression-free survival.) Eighty patients are also sufficient to estimate the best response rate to CHOP to within 11% (95% confidence interval). Sixty evaluable patients were expected to receive iodine I 131 tositumomab therapy and were sufficient to estimate the best response rate for patients receiving CHOP plus tositumomab/iodine I 131 tositumomab therapy to within 13% (95% confidence interval).

Eighty patients were sufficient to estimate the probability of any particular toxicity to within 11%. Any adverse event occurring with at least 5% probability was likely to be seen at least once (98% chance). Overall and progression-free survival curves were plotted by the method of Kaplan and Meier.[22]

Results

Patient characteristics

There were 102 patients registered to this trial between May 15, 1999, and June 1, 2000, when the study completed accrual and was closed. Twelve registered patients were ineligible, 7 owing to insufficient submission of prestudy information, 3 who did not have follicular lymphoma, 1 who had the wrong stage, and 1 who had a prior history of lymphoma. Fifty-two of the 90 eligible registrations (58%) were accrued by community-based hematologists and oncologists through community clinical oncology programs (CCOPs) or affiliate institutions, and 38 patients (42%) were treated at main member institutions (generally, major medical centers). The median time from diagnosis to treatment on this protocol was 36 days. The patient characteristics of the 90 eligible patients are shown in Table 1. The median age of patients on the trial was 50 years, with a range of 23 to 84 years. Fifty-five patients (61%) were male and 35 (39%) were female. Eighty-six patients (96%) were white; 2 (2%) were African American; and 2 (2%) were Hispanic. Twenty-three (27%) patients presented with "B" symptoms (fever, 10% weight loss, or drenching night sweats). Nineteen patients (23%) had bulky adenopathy. Five percent had stage II disease; 34% were stage III; and 62% were stage IV. As defined by the International Lymphoma Prognostic Index,[23] 47 patients (57%) were in the low-risk category, 29 (35%) were low-intermediate risk, 5 (6%) were high-intermediate risk, and 1 (1%) was high risk.

Protocol compliance

Eighty-six of 90 (96%) eligible patients completed CHOP treatment as planned. One eligible patient refused CHOP chemotherapy immediately after registration; this patient is coded as a major treatment deviation and is not assessable for CHOP toxicity. One eligible patient refused antibody therapy after receiving CHOP and is not assessable for antibody therapy toxicity. No follow-up information was submitted on 2 other patients. These patients are not assessable for either CHOP or antibody therapy toxicity. Two subjects discontinued protocol therapy early because of side effects (one grade 3 cardiac toxicity due to doxorubicin and one case of anaphylaxis with doxorubicin); one patient refused therapy unrelated to toxicity; and one did not complete the protocol for unknown reasons. Seventy-seven (90%) of the 86 patients who completed CHOP also completed antibody therapy. Thus, 77 (86%) of 90 eligible patients completed all protocol therapy. Only one of the patients who completed CHOP was removed from antibody therapy owing to toxicity. There is no record of any patient's receiving a reduced dose of tositumomab/iodine I 131 tositumomab

Table 1. Patient characteristics (N = 90)

Characteristics	
Median age, y (range)	50 (23-84)
Sex, n (%)	
Male	55 (61)
Female	35 (39)
Race, n (%)	
White	86 (96)
African American	2 (2)
Hispanic	2 (2)
Symptoms, n (%)	
A*	61 (73)
B†	23 (27)
Unknown	6
Histologic grade, n (%)	
I	50 (60)
II	24 (29)
III	9 (11)
Unknown	7
Bulky disease, n (%)	
Yes	19 (23)
No	63 (77)
Unknown	8
Stage, n (%)	
II	4 (5)
III	29 (34)
IV	53 (62)
Unknown	4
International prognostic index, n (%)[23]	
Low	47 (57)
Low-intermediate	29 (35)
High-intermediate	5 (6)
High	1 (1)
Unknown	8

*Absence of fever, weight loss, or night sweats.
†Fever, 10% weight loss, or drenching night sweats.

because of persisting thrombocytopenia following CHOP. Of the patients who received tositumomab/iodine I 131 tositumomab, 74% received it as outpatients, and 26% received it as inpatients. For the 90 eligible patients, 380 bone marrow specimens were submitted (4.2 bone marrow specimens per patient), indicating excellent compliance with the tissue submission and restaging objectives of the protocol.

Toxicities due to CHOP

Protocol treatment was well tolerated in the majority of the 87 patients evaluated for CHOP toxicity. Thirty-four patients (39%) experienced, at worst, grade 4 toxicity, and 29 patients (33%), at worst, grade 3 toxicity during the chemotherapy phase (Table 2). Reversible hematologic toxicities constituted most of the adverse events, including grade 4 hematologic toxicities in 31 (36%) and grade 3 hematologic toxicities in 24 (28%) patients. Specifically, 31 patients (36%) had grade 4 neutropenia; 14 (16%) experienced grade 3 neutropenia; 1 (1%) had grade 3 thrombocytopenia; and 3 (3%) had grade 3 anemia. One patient (1%) had a grade 4 infection, and 11 patients (13%) experienced grade 3 infections. Five of the 11 grade 3 infectious events were febrile neutropenia, as was the only grade 4 infectious event. One patient (1%) developed grade 4 stomatitis, and 6 patients (7%) experienced grade 3 gastrointestinal toxicities (mainly nausea and vomiting). Six (7%) patients experienced grade 3 neuropathy; 4 (5%) had grade 3 cardiovascular toxicity; 1 (1%) had grade 4 cardiovascular toxicity; and 1 (1%) developed grade 4 edema. One of the cardiac toxicities was grade 3 congestive heart failure. Four patients received red blood cell transfusions during CHOP therapy.

Toxicities due to tositumomab/iodine I 131 tositumomab

Toxicities observed after tositumomab/iodine I 131 tositumomab were generally milder than those seen after CHOP. Only 10 of 82 eligible patients receiving antibody therapy experienced, at worst, grade 4 toxicities (12%) and 28 experienced, at worst, grade 3 toxicities (34%). Most of the grade 3 and 4 toxicities were reversible cytopenias, including those experienced by 5 patients (6%) with grade 4 neutropenia, 2 (2%) with grade 4 thrombocytopenia, and 2 (2%) with grade 4 anemia (Table 2). In this particular trial, we were unable to identify any pretreatment parameters that predicted myelotoxicity. One patient (1%) experienced a grade 4 anaphylactoid reaction during the dosimetric infusion of unlabeled tositumomab and did not receive iodine I 131 tositumomab. One subject (1%) developed grade 4 lower back pain and chest heaviness. No patient was reported with symptoms of serum sickness after antibody administration. Transfusions of red cells were given to 2 patients (2%) following tositumomab/iodine I 131 tositumomab, and 3 (3%) received platelet transfusions. Only 2 (2%) grade 4 and 13 (16%) grade 3 nonhematologic toxicities were

Table 2. Grades 3 to 5 toxicities (expressed as % of evaluable patients)

	After CHOP; n = 87			After tositumomab/iodine I 131 tositumomab; n = 82		
Toxicity by worst grade	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Neutropenia	14	31	0	8	5	0
Thrombocytopenia	1	0	0	9	2	0
Anemia	3	0	0	0	2	0
Gastrointestinal	6	1	0	1	0	0
Dermatologic	0	0	0	2	0	0
Flu-like symptoms	2	0	0	2	0	0
Pulmonary	2	0	0	0	0	0
Infection	11	1	0	2	0	0
Neurologic	6	0	0	1	0	0
All endocrine	0	0	0	0	0	0
Cardiovascular	4	1	0	0	0	0
Renal	1	0	0	0	0	0
Sexual/reproductive	2	0	0	1	0	0
Pain	3	0	0	2	1	0
Immunologic	0	1	0	0	1	0
Total	30	34	0	28	10	0

observed with tositumomab/iodine I 131 tositumomab (Table 2). The cytopenias observed on this protocol were generally asymptomatic and required no intervention in most patients. Only 31 (38%) received filgrastim or sargramostim and only 5 (6%) received erythropoietin at any point during their course; in most cases, growth factors were given during CHOP therapy, not following radioimmunotherapy.

Delayed toxicities

One case of myelodysplasia occurred 16 months after registration, and one patient developed breast cancer 32 months after registration to this study. In 3 of 41 patients (7%) for whom serial testing was available (grade 2 thyroid toxicity), elevated TSH levels developed: at 6, 12, or 24 months after tositumomab/iodine I 131 iodine-tositumomab therapy. None of the patients experienced symptomatic hypothyroidism, but thyroid hormone replacement therapy was initiated in these cases.

Responses

Among the 90 eligible patients, 7 were not assessable for remission status, either because insufficient data were submitted to evaluate responses (6 cases) or because protocol therapy was not administered (1 case). Eighty-one (90%) of the 90 eligible patients achieved documented objective remissions after CHOP plus tositumomab/iodine I 131 tositumomab, including 49 (54%) complete remissions (CRs), 11 (12%) unconfirmed complete remissions (CRu's), and 21 (23%) partial remissions (PRs). Two patients (2%) had stable disease. Forty-three percent of patients continued to have bone marrow involvement with lymphoma after CHOP and before tositumomab/iodine I 131 tositumomab. If responses were assessed only for the 83 registered patients for whom sufficient documentation was available to assess response, 98% had objective remissions (PR plus CR plus CRu), including 59% CRs, 13% CRu's, and 25% PRs.

Therapy with tositumomab/iodine I 131 tositumomab substantially improved overall best response (Table 3). Among the 47 fully assessable patients with a PR or CRu to CHOP for whom data are available on the response after each stage of the regimen, the addition of tositumomab/iodine I 131 tositumomab improved overall best response in 27 patients (57%), either from a PR to a CRu or CR (n = 23, 49%), or from a CRu to a CR (n = 4, 9%).

Table 3. Responses to therapy

Response	After CHOP, n (%)	After CHOP + tositumomab/iodine I 131 tositumomab,* n (%)
Complete remission	24 (27)	49 (54)
Complete remission, unconfirmed	11 (12)	11 (12)
Partial remission	44 (49)	21 (23)
Stable disease	2 (2)	2 (2)*
Not evaluable†	9 (10)	7 (8)
Total	90 (100)	90 (100)

*Patients who did not achieve a PR, CRu, or CR with CHOP were not eligible to receive tositumomab/iodine I 131 tositumomab.

†Incomplete restaging (CT scans, bone marrow [BM] biopsies, etc) was performed on 9 patients after completion of CHOP, rendering them inevaluable for response assessment. Two of these 9 patients had complete restaging after completion of antibody therapy, but 7 remained inevaluable for response after completion of the entire program.

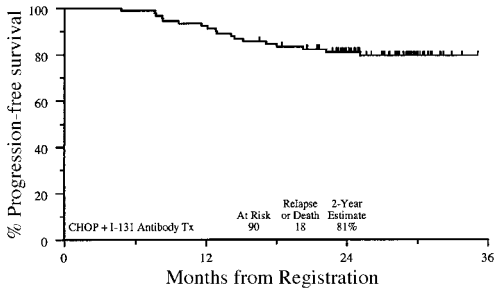

Figure 1. Failure-free survival of 90 eligible patients with stages II to IV follicular non-Hodgkin lymphoma treated with 6 cycles of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab.

Progression-free and overall survival

All 90 eligible patients registered to this trial are evaluable for progression-free and overall survival. With a median follow-up of 2.3 years, 18 of 90 eligible patients have experienced relapse (n = 14) or have died (n = 4) for an estimated 2-year progression-free survival (PFS) of 81% (Figure 1). Four eligible patients (4%) have died: 2 of progressive lymphoma, 1 of apparent myocardial infarction unrelated to treatment, and 1 of sepsis after disease progression and receipt of additional nonprotocol therapy. None of these deaths were considered related to the treatment given on this protocol. The 2-year estimate of overall survival was 97% (Figure 2).

Discussion

This study has established the feasibility, tolerability, and efficacy of sequential therapy with 6 cycles of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab as primary therapy for patients with advanced follicular lymphoma. Patients up to age 84 years tolerated the treatment regimen well. Most grade 3 and 4 toxicities occurred during the CHOP segment of the treatment program and were reversible. Tositumomab/iodine I 131 tositumomab was successfully administered in the community by practicing oncologists and hematologists; only 2 patients experienced toxicities that precluded completion of CHOP therapy, and only 1 patient experienced toxicity that precluded completion of antibody therapy. Hematologic toxicity was moderate with tositumomab/iodine I 131 tositumomab following 6 cycles of CHOP and rarely led to serious infections or required transfusion support.

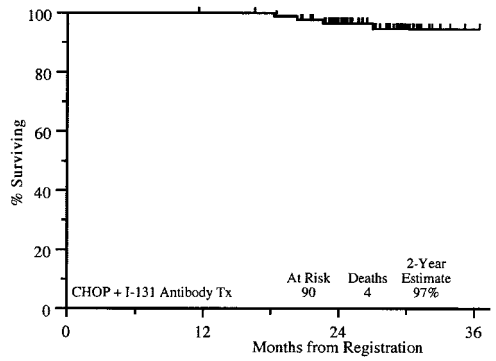

Figure 2. Overall survival of 90 eligible patients with stages II to IV follicular non-Hodgkin lymphoma treated with 6 cycles of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab.

The choice of first-line chemotherapy for the treatment of patients with advanced follicular lymphoma remains controversial. CHOP was chosen for this study for the following reasons. First, the use of a moderately aggressive regimen such as CHOP was deemed most likely to produce a state of minimal tumor burden, which was considered the ideal setting for immunotherapy. Second, other adjuvant immunotherapies (eg, interferon-alpha) have been shown to produce an advantage in terms of progression-free or overall survival only in studies using aggressive doxorubicin-containing chemotherapy regimens such as CHOP and not when combined with regimens such as chlorambucil or CVP.[8] Finally, a pilot trial by Czuczman et al[9] combining CHOP chemotherapy with concurrent rituximab demonstrated a promising 95% overall response rate and a 75% 2-year progression-free survival in newly diagnosed patients with advanced follicular lymphoma. Since the Czuczman regimen of CHOP plus rituximab has been chosen as 1 of 2 arms on the phase 3 randomized SWOG trial (S0016) for which this study was a pilot, it was necessary (for parallelism) to administer CHOP with the radioimmunotherapy arm also. Sequential administration of CHOP followed by tositumomab/iodine I 131 tositumomab was necessary because of additive severe myelosuppression anticipated with concurrent administration of these 2 therapies.

The choice of radiolabeled antibody for this study was also a subject of debate. Two commercial radiolabeled antibody products have undergone extensive testing in non-Hodgkin lymphoma, namely, tositumomab/iodine I 131 tositumomab and rituximab/yttrium-90 ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals, San Diego, CA). Hundreds of patients with relapsed or refractory B-cell lymphomas have been treated with both products, and the response rates and types of toxicities have been similar. We elected to employ tositumomab/iodine I 131 tositumomab for this study because of the substantially longer follow-up of patients treated with this radioimmunotherapy (which has been in clinical trials since 1990) and because of theoretic considerations regarding the physical characteristics of I-131 and yttrium 90 (Y-90). The beta particles emitted by I-131 deposit their energy within a radius only one fifth as large as that of Y-90 (0.9 mm versus 5 mm). Consequently, some investigators have hypothesized, on the basis of computer modeling, that iodine-131 may be more effective for small tumor nodules than yttrium-90.[24] Since patients entered on this trial were cytoreduced with 6 cycles of CHOP prior to radioimmunotherapy, tositumomab/iodine I 131 tositumomab was considered preferable for this protocol.

Despite initial controversy about the optimal regimen for this study, it is apparent that the regimen selected was very effective. Eighty-one of the 83 eligible subjects (98%) for whom sufficient follow-up data were available to analyze responses obtained objective remissions with CHOP followed by tositumomab/iodine I 131 tositumomab. More importantly, among the 47 fully assessable patients who achieved a PR or CRu with CHOP, 27 (57%) improved their remission status after treatment with tositumomab/iodine I 131 tositumomab. Toxicities were generally mild, although longer follow-up is necessary to ascertain the risks of stem cell damage, myelodysplasia, and acute leukemia. The progression-free (81%) and overall survival rates (97%) observed with this regimen compare favorably to the best reported results obtained with follicular lymphoma.[5,9] Furthermore, the PFS obtained on this study appears promising compared with that obtained in SWOG's preceding studies using CHOP alone[5] or with the PFS obtained in a phase 2 study of follicular lymphoma (S9800) in which patients received 6 cycles of CHOP followed by 4 weekly doses of rituximab.[11] These findings suggest that this novel regimen is a good candidate for study in a randomized setting to determine if it is superior to other therapies for follicular lymphoma. Such a randomized study is currently underway under the auspices of the Southwest Oncology Group and Cancer and Leukemia Group B (S0016). This ongoing randomized trial compares CHOP followed by tositumomab/iodine I 131 tositumomab given exactly as in this study with 6 cycles of CHOP given concurrently with rituximab according to the regimen devised by Czuczman.[9]

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Appendix

Patients in the study were treated at the following SWOG-affiliated institutions: Columbus CCOP, Columbus, OH; Virginia Mason CCOP, Seattle, WA; Columbia River CCOP, Portland, OR; Montana CCOP, Billings, MT; University of Utah, Salt Lake City; University of Arkansas, Little Rock; Dayton CCOP, Dayton, OH; University of Hawaii, Honolulu; Highlands Oncology Group/Washington Regional Medical Center, Springdale, AR; Kansas City CCOP, Kansas City, MO; Providence Hospital, Washington, DC; St. Louis CCOP, St. Louis, MO; City of Hope Medical Center, Duarte, CA; INTEGRIS Oncology, University of Oklahoma, Oklahoma City; San Juan Regional Medical Center, University of New Mexico, Farmington; Santa Rosa CCOP, Santa Rosa, CA; St. Francis Hospital/Stormont-Vail HealthCare, Topeka, KS; Sutter Health Western Division Cancer Research Group, Greenbrae, CA; Upstate Carolina CCOP, Spartanburg, SC; Wichita CCOP, Wichita, KS; Akron General Medical Center/Cleveland Clinic, Akron, OH; Cottage Health Systems, Santa Barbara, CA; Holy Family Hospital, Spokane, WA; Meridia Hillcrest Hospital, Mayfield Heights, OH; Northwest CCOP, Tacoma, WA; Ozarks Regional CCOP, Springfield, MO; Pheobe Putney Memorial Hospital, Albany, GA; Thibodaux Hospital, Thibodaux, LA; West Florida Medical Center, Pensacola, FL.

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