Published in final edited form as:

Pediatr Blood Cancer. 2009 February ; 52(2): 177–181. doi:10.1002/pbc.21753.

A Study of Rituximab and Ifosfamide, Carboplatin, and Etoposide Chemotherapy in Children with Recurrent/Refractory B-cell (CD20+) Non-Hodgkin Lymphoma and Mature B-Cell Acute Lymphoblastic Leukemia: A Report from the Children's Oncology Group

Timothy C. Griffin, MD¹, Sheila Weitzman, MD², Howard Weinstein, MD³, Myron Chang, PhD⁴, Mitchell Cairo, MD⁵, Robert Hutchison, MD⁶, Bruce Shiramizu, MD⁷, Joseph Wiley, MD⁸, Deborah Woods⁹, Margaret Barnich¹⁰, and Thomas G. Gross, MD, PhD¹¹

¹Memorial Hospital of South Bend, South Bend, IN

²Hospital for Sick Children, Toronto, Ontario, Canada

³Massachusetts General Hospital, Boston, MA

⁴Statistics, Children's Oncology Group, Gaines, FL

⁵Columbia Presbyterian College of Physicians and Surgeons, New York, NY

⁶State University of New York at Syracuse, Syracuse, NY

⁷Cancer Research Center of Hawaii, Honolulu, HI

⁸Sinai Hospital of Baltimore, Baltimore, MD

⁹Nursing, Sutter Medical Center, Sacramento, CA

¹⁰C.S. Mott Children's Hospital, Ann Arbor, MI

¹¹ Nationwide Children's Hospital, Columbus, OH

Abstract

Background—To estimate the response rate and therapy related toxicities of the anti-CD20 monoclonal antibody rituximab when combined with chemotherapy including ifosfamide, carboplatin, and etoposide (ICE) in patients with relapsed and refractory B-cell non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia (B-ALL).

Methods—Patients received rituximab and ICE for 1 to 3 cycles, depending upon response. Rituximab (375 mg/m²) was given on day 1 and 3 of each cycle (day 1 only for cycle 3), with ifosfamide (3000 mg/m²) and etoposide (100 mg/m²) given on days 3, 4, and 5 and carboplatin (635 mg/m²) given on day 3 only.

Results—Twenty-one patients were enrolled, of whom 20 were eligible and evaluable. Although hematologic toxicities were common, only one patient was removed from study due to prolonged myelosuppression. Toxicities related to infusions of rituximab were frequent but manageable. Of the 6 eligible patients with diffuse large B-cell lymphoma, 3 achieved complete remission (CR), 1 had stable disease (SD), and 2 had progressive disease (PD). Of the 14 eligible patients with Burkitt lymphoma and B-ALL, there were 4 complete responses (CR), 5 partial responses (PR), 1

SD and 4 with PD. Thus the CR/PR rate for the entire group was 12/20 (60%). Following completion of protocol therapy 6 patients were able to proceed to consolidation with high-dose therapy and stem cell rescue.

Conclusions—The combination of rituximab and ICE chemotherapy was associated with an encouraging objective response rate and an acceptable toxicity profile.

Keywords

Non-Hodgkin's Lymphoma; Large Cell Lymphoma; Burkitt's Lymphoma; Chemotherapy

Introduction

Outcome for children with mature B-cell (CD20+) lymphomas has improved in the last few decades. Patients with localized or CNS-negative advanced-stage Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) have a greater than 90% chance of survival, while patients with more advanced, high-risk disease (CNS positive and/or mature B-cell acute lymphoblastic leukemia) have survivals in the range of 80-90%. (1,2) Patients with primary refractory disease or those who experience relapse, however, have a much poorer prognosis. (3-8) Many such patients are refractory to retrieval therapy or die of complications while attempting to achieve a second remission. Novel strategies are needed to increase the proportion of patients who achieve at least a partial remission to retrieval therapy so that they may have an opportunity to proceed to potentially curative high-dose therapy with stem cell rescue. (9)

The development of targeted, monoclonal antibodies has provided new promise for patients with B-cell malignancies. We have previously demonstrated that CD20 is expressed in greater than 98% of childhood BL and DLBCL. (10) CD20 is an excellent surface target and neither sheds, modulates, or is internalized, and the chimeric monoclonal anti CD20 antibody, rituximab, was initially approved for the treatment of adults with indolent B-cell non-Hodgkin's lymphoma (B-NHL). Subsequently, the addition of rituximab to CHOP chemotherapy was demonstrated to improve both the event-free survival and overall survival compared to CHOP chemotherapy alone in both the elderly and younger adults with DLBCL. (11,12) Additional studies in adults have demonstrated promising activity of rituximab when added to a variety of other chemotherapy regimens in both newly-diagnosed and refractory patients with DLBCL. (13,14) Preliminary results of regimens utilizing rituximab and intensive multiagent chemotherapy for adults with newly-diagnosed BL have been encouraging. (15) The use of rituximab with or without chemotherapy in pediatric patients with B-NHL, however, has been limited to anecdotal and preliminary reports. (16,17)

The chemotherapy combination which includes ifosfamide, carboplatin, and etoposide (ICE) is commonly employed for retrieval therapy for pediatric patients with refractory/relapsed B-cell malignancies. (6,7) The Children's Oncology Group therefore designed a phase II pilot study, ANHL0121, to assess the toxicity and efficacy of ICE when used in combination with rituximab in children and adolescents with recurrent/refractory B-NHL and mature B-ALL.

Methods

Eligibility Criteria

Eligible patients included those <21 years of age with relapsed or primarily refractory CD20+ non-Hodgkin lymphoma (NHL, any histology) or mature B-cell acute lymphoblastic

leukemia (B-ALL). Because of concerns regarding potential excess toxicity, patients with HIV-1 and active hepatitis B infection were excluded. Other eligibility criteria included performance status of 0, 1, or 2, life expectancy ≥ 2 months, and recovery from all acute toxic effects of prior therapy. Renal insufficiency was allowed only if felt to be acute and related to tumor lysis. Patients with isolated CNS disease were not eligible.

Institutional review boards at individual participating institutions approved the study, with written informed consent obtained from patients ≥ 18 years of age.

Treatment Plan

Intravenous (IV) hydration and alkalinization were instituted, with treatment of hyperuricemia with rasburicase or allopurinol at the investigator's discretion. Up to three courses of therapy were administered, depending on disease response (see below). Rituximab (375 mg/m^2) was given IV on days 1 and 3 of courses 1 and 2, and on day 1 only of course 3, if administered. Thus, the first dose of rituximab was given 2 days prior to the start of the chemotherapeutic agents with each course. This schedule was chosen in order to assure adequate serum levels of rituximab in the event patients presented with bulky, advanced disease. Patients were premedicated with acetaminophen and diphenhydramine. Corticosteroids were also permitted for acute hypersensitivity reactions and as premedication for subsequent courses.

Chemotherapy consisted of ifosfamide, 3000 mg/m^2 as a 2 hour IV infusion daily on days 3, 4 and 5. Adequate hydration was assured with pre- and post-hydration, with frequent voiding required. Mesna, 600 mg/m^2 was mixed with the dose of ifosfamide and also given as 15 minute IV boluses 3, 6, 9, and 12 hours after the start of the ifosfamide. Mesna was changed to continuous 24 hour infusion if microscopic or gross hematuria occurred. Etoposide, 100 mg/m^2 was given daily as a 1 hour IV infusion on days 3, 4, and 5, administered in concentration $< 0.4 \text{ mg/ml}$ to prevent precipitation. Carboplatin, 635 mg/m^2 (no maximum dose) was given as a 1 hour IV infusion on day 3 only. Antiemetic support was at the individual treating physician's discretion, although corticosteroids were not allowed as antiemetics.

Intrathecal (IT) therapy with methotrexate and cytarabine was administered in the following age-dependent doses, respectively: $0 < 2$ yrs, 8 mg and 16 mg; $2 > 3$ years, 10 mg and 20 mg; $3 < 9$ years 12 mg and 24 mg; > 9 years 15 mg and 30 mg. Patients with CNS disease, with any histology, received IT therapy on days 3, 10, and 17 of courses 1 and 2. Patients with large cell lymphoma who were CNS negative received IT therapy on day 3 of course 1 only. Patients with BL and B-ALL who were CNS negative received IT therapy on day 3 of each cycle given.

Growth factor support with granulocyte-colony stimulating factory (G-CSF) was begun on day 6 of each course. The dosage was $5 \text{ } \mu\text{g/kg/day}$ unless peripheral blood stem cell (PBSC) collection was contemplated, in which case the dose was raised to $10 \text{ } \mu\text{g/kg/day}$.

Patients underwent an evaluation of disease status after each course of therapy. The response criteria used were based on those for adult NHL. (18) Patients experiencing progressive disease (PD) at any time were ineligible to receive further study therapy. Patients who achieved a complete remission (CR) with course 1 received a second course and were then off therapy, with the expectation that high-dose therapy with stem cell transplantation might be considered at that point. Patients with partial remission (PR) or stable disease (SD) after course 1 also received a second course. A third course of therapy was only allowed if those patients continued to show objective disease response and improvement (achieved a CR or PR) after course 2. Patients with SD or those with continued marrow involvement after

course 2 were not to receive course 3. Criteria for proceeding with the next course were elapsed time 23 days from the start of the previous course, resolution of grade 3 or 4 toxicities, and control of any infectious complications. Marrow recovery (ANC > 1,000/ μ L and off G-CSF >48 hours, and platelet count >100,000/ μ L) was required, although these requirements could be waived in the face of marrow involvement at study entry. Prolonged myelosuppression or failure of resolution of toxicities causing treatment delays > 2 weeks were criteria for removal from protocol therapy. PBSC collection was not mandated but, if performed, data regarding the CD34+ cell count yield was obtained.

Statistical Methods

The study objective was to determine whether the protocol therapy achieved objective response (OR) rates greater than for ICE chemotherapy alone. Based on historical data, this response rate was determined to be 0.51. Initially, a two-stage analysis was planned, with two different disease strata: DLBCL and BL/B-ALL. (19,20) The first stage would enroll 21 patients in each stratum. If there were 9 or fewer OR in each stratum, it would be concluded that the protocol therapy was not superior, and that stratum closed. If there were 10 or more OR, an additional 20 patients would be enrolled (41 patients total per stratum), with 23 OR needed to conclude superiority. As the study progressed, it became evident that accrual goals would not be met and the accrual was stopped earlier than initially planned. The response rate (CR or PR) was estimated by a 95% confidence interval. Distributions of overall survival (OS) were estimated by the Kaplan-Meier method. The difference in OS between patients who responded to the treatment and patients who did not respond to the treatment was assessed by the logrank test.

Results

Patients

A total of 21 patients were entered on the trial. Following study entry one patient was found to have evidence of active hepatitis B infection and per eligibility criteria was removed from study, although this patient did not exhibit any apparent hepatic toxicity with treatment. Of the 20 eligible patients, 6 (30%) had DLBCL, 12 (60%) had BL, and 2 (10%) had B-ALL (one with concomitant CNS involvement). All patients presented with recurrent disease following an initial response to therapy. Clinical information regarding the patients, including sites of involvement, number of courses delivered, maximal response, CD34+ cell yield (if PBSC collection performed), and follow-up data are contained in Tables I and II.

Toxicity

A total of 41 treatment courses were delivered to eligible patients. As expected, severe myelosuppression was nearly universal, but reversible. Only one patient was removed from study because of an excessive delay (> 2 weeks) before the next scheduled course due to persistent low counts; this patient had B-ALL and had relapsed in the marrow at the end of initial treatment. Infections were also common but manageable; no patient died of infection. Grade 2-4 allergic reactions (fever, rash, chills, hypotension) associated with rituximab infusion were reported in 6 of the 41 treatment courses. All patients were able to continue with further infusions with premedication, with only one reaction reported after the initial infusion. No other unusual or unexpected toxicities were encountered (Table III).

Response

Objective responses (PR/CR) were noted in 12 of 20 (60%, with a 95% confidence interval from 39% to 81 %) of the total group, 3/6 (50%, all CR) in the DLBCL group and 9/14

(64%, 4 CR, 5 PR) in the BL/B-ALL group. Of the non-responders, 2 were reported to have stable disease and 6 had disease progression during treatment.

Outcome Following Protocol Therapy

A Kaplan-Meier plot of overall survival of the 20 eligible patients is shown in Figure 1. Patients who responded to the treatment had significantly longer OS (2-sided $p = 0.0001$) than patients who did not respond to the treatment (Figure 2). The 8 non-responding patients had poor outcome, with no survivors and very short (2.5 month) median survival from study entry. Of the 12 responders, however, 8 were reported to be alive (one with disease) with follow-up of 13-30 months. Most of the survivors, 5 of 8, received high-dose therapy with stem cell transplantation (SCT), although 2 of the patients with DLBCL survive without SCT. All 4 patients with Burkitt and B-ALL who survive without disease received SCT (3 auto, 1 allo transplant). Five of the six patients who ultimately received SCT (4 auto, 2 allo), are survivors.

CD34+ Cell Yield with PBSC Collection

A total of six patients responding to therapy underwent PBSC collection immediately following a course of treatment. In 5 of 6, greater than the 2×10^6 CD34+ cells/kg target threshold were collected (Tables I and II).

Discussion

During the past two decades there has been a steady improvement in the outcome for children and adolescents with high-grade B-cell malignancies. Contemporary therapies provide a high likelihood of survival for most newly-diagnosed patients. (1-3,8) Despite this remarkable success story, the outcome for individuals who have refractory disease initially or for those who relapse is dismal. Cairo et al reported a 12% post event survival in patients with Burkitt lymphoma diagnosed from 1977-1997; details of retrieval therapy were unknown in that cohort. (3) In the Children's Cancer Group study 5912 the DECAL regimen was given to 68 patients with recurrent NHL with a 50% response rate which was independent of histologic subtype. Overall survival was 33% at 2 years but only 2 of 13 patients with Burkitt lymphoma were described as long-term survivors. (5) Kung et al reported a 71% CR/PR rate in a Pediatric Oncology Group trial of 21 patients with recurrent NHL using ICE chemotherapy, and Cairo et al reported response in 4 of 6 patients with lymphoma using a slightly more dose-intensive ICE regimen. Neither of those trials included a breakdown of the study population by histology, however, and long-term outcomes were not reported. (6,7) Nevertheless, perhaps in part because of the encouraging results of those studies ICE has become a commonly employed salvage regimen pediatric patients with relapsed NHL.

The small number of patients enrolled in the present study preclude definitive conclusions regarding the therapeutic efficacy of the combination of rituximab and ICE chemotherapy. Nonetheless, the response rate observed (60%) appears to be at least comparable to previous reports of other salvage regimens, and is especially impressive in view of the prior, intensive contemporary treatments received by the patients. Many with objective responses were able to proceed to consolidative therapy with SCT, and the proportion of patients still alive and free of disease at last follow-up is larger than in any previously published series of such patients. Intriguingly, in the DLBCL group, 2 of the survivors did not receive high-dose consolidation therapy with SCT.

Patients enrolled in this trial had a very short survival if they did not respond to salvage therapy, while those with chemo-responsive disease had a chance at successful retrieval.

Thus, with what is perhaps more effective relapse therapy, the correlation between response to initial retrieval therapy and survival, seen in other diseases such as Hodgkin lymphoma, may now be evident with high-grade B-cell malignancies as well.

The commercial availability of rituximab has provided the opportunity to combine it with chemotherapy combinations, such as ICE, for use in relapsed or refractory high-grade B-cell lymphoma outside the setting of a clinical trial. The current study is important because it provides controlled data regarding tolerability of the regimen as well as some response data. The combination of rituximab and ICE chemotherapy was delivered without unexpected or excessive toxicity. Infusion-related toxicities were encountered but manageable, and no patient experienced cytokine release reactions that have been reported in patients with advanced disease. (21) There was no evidence of exaggerated hematologic toxicity with the regimen, despite the intensive previous therapies received by the many of the enrolled patients. Despite the potential for augmented immunosuppression due to the B-cell depletion by rituximab, the number, type, and severity of infections encountered were not greater than what would be expected with ICE chemotherapy alone. Finally, the regimen was effective as a stem cell mobilization regimen for most patients who underwent stem cell collection.

The role of rituximab in the treatment of pediatric B-NHL remains an active area of investigation. The COG is currently exploring the use of rituximab in combination with the intensive chemotherapy regimen used in the most recent multinational cooperative study, (1,2) and in combination with cyclophosphamide and prednisone for patients with post-transplant lymphoproliferative disease. Rituximab, combined with ICE chemotherapy, could be considered for incorporation into upfront therapy regimens, although the excellent outcome for most patients would make it difficult, from a statistical standpoint, to prove improvement over current upfront therapy in a controlled trial. The tolerance and encouraging response rate of rituximab and ICE in the current trial suggest that this combination represents a reasonable treatment approach for patients with DLBCL, Burkitt lymphoma, and mature B-ALL who have failed primary therapy.

Acknowledgments

A complete listing of grant support for research conducted by CCG and POG before initiation of the COG grant in 2003 (CA 98543) is available online at: <http://www.childrensoncologygroup.org/admin/grantinfo.htm>

REFERENCES

1. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. *Blood*. 2007; 109:2773–2780. [PubMed: 17132719]
2. Cairo MS, Gerrard M, Spoto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. *Blood*. 2007; 109:2736–2743. [PubMed: 17138821]
3. Cairo MS, Spoto R, Perkins SL, et al. Burkitt's and Burkitt-like lymphoma in children and adolescents: a review of the Children's Cancer Group experience. *Br J Haematol*. 2003; 120:660–670. [PubMed: 12588354]
4. Gentet JC, Patte C, Quintana E, et al. Phase II study of cytarabine and etoposide in children with refractory or relapsed non-Hodgkin's lymphoma: A study of the French Society of Pediatric Oncology. *J Clin Oncol*. 1990; 8:661–665. [PubMed: 2313335]
5. Koberinsky NL, Spoto R, Shah NR, et al. Outcomes of treatment of children and adolescents with recurrent non-Hodgkin's lymphoma and Hodgkin's disease with dexamethasone, etoposide, cisplatin, cytarabine, and l-asparaginase, maintenance chemotherapy, and transplantation: Children's Cancer Group Study CCG-5912. *J Clin Oncol*. 2001; 19:2390–2396. [PubMed: 11331317]

6. Kung FH, Harris MB, Krischer JP. Ifosfamide/carboplatin/etoposide (ICE), an effective salvaging therapy for recurrent malignant non-Hodgkin lymphoma of childhood: a Pediatric Oncology Group phase II study. *Med Pediatr Oncol.* 1999; 32:225–226. [PubMed: 10064193]
7. Cairo MS, Krailo M, Miser J, et al. Prospective randomized trial between two doses of granulocyte colony-stimulating factor after ifosfamide, carboplatin, and etoposide in children with recurrent or refractory solid tumors: a children's cancer group report. *J Pediatr Hematol Oncol.* 2001; 23:30–38. [PubMed: 11196267]
8. Cairo MS, Spoto R, Hoover-Regan M, et al. Childhood and adolescent large cell lymphoma (LCL): a review of the Children's Cancer Group experience. *Am J Hematol.* 2003; 72:53–63. [PubMed: 12508269]
9. Philip T, Harnmann O, Pinkerton R, et al. Curability of relapsed childhood B-cell non-Hodgkin's Lymphoma after intensive first line therapy: A report from the Societe Francaise d'Oncologie Pediatrique. *Blood.* 1993; 81:2003–2006. [PubMed: 8471762]
10. Perkins SL, Lones MA, Davenport V, Cairo MS. B-cell non-Hodgkin's lymphoma in children and adolescents: Surface antigen expression and clinical implications for future targeted bioimmune therapy. A Children's Cancer Group report. *Clin Adv Hematol Oncol.* 2003; 1:314–317. [PubMed: 16224429]
11. Feugier P, van Hoof A, Sebban C, et al. Long term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol.* 2005; 23:4117–4126. [PubMed: 15867204]
12. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: A randomized controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2006; 7:379–391. [PubMed: 16648042]
13. Ladetto M, Zallio F, Vallet S, et al. Concurrent administration of high-dose chemotherapy and rituximab is a feasible and effective chemo/immunotherapy for patients with high-risk non-Hodgkin's lymphoma. *Leukemia.* 2001; 15:1941–1949. [PubMed: 11753616]
14. Garcia-Suarez J, Banas H, Arribas I, et al. Dose-adjusted EPOCH plus rituximab is an effective regimen in patients with poor-prognostic untreated diffuse large B-cell lymphoma: results from a prospective observational study. *Br J Haematol.* 2007; 136:276–285. [PubMed: 17233819]
15. Thomas D, Faderl S, O'Brien S, et al. Chemoimmunotherapy with Hyper CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer.* 2006; 106:1569–1580. [PubMed: 16502413]
16. Culic S, Culic V, Armanda V, et al. Anti-CD20 monoclonal antibody (rituximab) for therapy of mediastinal CD20-positive large B-cell non-Hodgkin lymphoma with a local tumor extension into the lung of a 10-year-old girl. *Pediatr Hematol Oncol.* 2003; 20:339–344. [PubMed: 12746167]
17. deVries MJ, Veerman AJP, Zwaan CM. Rituximab in three children with relapsed/refractory B-cell acute lymphoblastic leukaemia/Burkitt non-Hodgkin's lymphoma. *Br J Haematol.* 2004; 125:414–415. [PubMed: 15086431]
18. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol.* 1999; 17:1244–1253. [PubMed: 10561185]
19. Chang MN, O'Brien PC. Confidence intervals following group sequential tests. *Controlled Clinical Trials.* 1987; 7:18–26. [PubMed: 3956209]
20. Chang MN, Therneau TM, Wieand HS, et al. Designs for group sequential phase II clinical trials. *Biometrics.* 1987; 43:865–874. [PubMed: 3427171]
21. Winkler U, Schulz HR, Klein TO. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood.* 1999; 94:2217–2224. [PubMed: 10498591]

Figure 1.
Overall Survival: All Eligible Patients

Figure 2.
Overall Survival: Responders vs. Non-Responders.

Table 1

Clinical Information for Patients with Large Cell Lymphoma

Patient #	Sex	Age (yr)	Sites of Involvement	# Courses	Response	CD 34+ Yield/kg	Status	Follow-Up (mos)	SCT
2	M	17	Neck	3	CR	5.3×10^6	Alive, NED	30+	No
3	F	11	Multiple Nodes	1	PD	ND	DOD	3	No
10	M	15	Abdomen	1	PD	ND	DOD	8	No
12	M	17	Mediastinum	3	SD	ND	DOD	10	Yes (allo)
17	M	20	Mediastinum, Abdomen	3	CR	ND	Alive, NED	15+	Yes (auto)
20	M	15	Nasopharynx, Neck	3	CR	4.5×10^6	Alive, NED	13+	No

CR: Complete Response; SD: Stable Disease; PD: Progressive Disease; ND: Not Performed; NED: No Evidence of Disease; DOD: Died of Disease; SCT: Stem Cell Transplant

Table II

Clinical Information for Patients with Burkitt Lymphoma and B-ALL

Patient #	Sex	Age (yr)	Sites of Involvement	# Courses	Response	CD 34+ Yield/kg	Status	Follow-Up (mos)	SCT
1	F	9	BM, CNS	1	PD	ND	DOD	1	No
4	M	5	BM	1	SD	ND	DOD	1	No
5	F	16	Liver, Kidney, Pelvis	3	PR	0.1×10^6	DOD	12	No
6	M	5	BM	3	CR	11×10^6	Alive, NED	30+	Yes (auto)
7	M	14	BM, Hilar Nodes	2	PR	ND	DOD	1	No
8	M	15	Abdomen	3	PR	19.9×10^6	Alive, NED	26+	Yes (auto)
9	M	11	Pleural Effusion, Bladder	1	PD	ND	DOD	1	No
11	M	10	Pelvis, Mandible	1	PD	ND	DOD	2	No
13	M	20	Axillary Nodes	3	CR	ND	Alive, DZ	14+	No
14	M	9	Abdominal Wall, Pelvis	1	PD	ND	DOD	3	No
15	F	13	BM, Abdomen	2	CR	ND	Alive, NED	18+	Yes (auto)
16	M	16	BM, Brachial Plexus	2	CR	ND	Alive, NED	20+	Yes (allo)
18	M	5	Liver, Kidney, CNS	1	PR	ND	DOD	4	No
21	M	14	Mediastinum, Abdomen, CNS	3	PR	2.2×10^6	DOD	11	No

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; BM: Bone Marrow; CNS: Central Nervous System; ND: Not Performed; NED: No Evidence of Disease; DOD: Died of Disease; DZ: With Disease; SCT: Stem Cell Transplant

Table III**Reported Toxicities**

Targeted Toxicities	Grade 3	Grade 4	All Grades
Neutrophils	1	3	36
Platelets	1	4	37
Allergy/Hypersensitivity	5	0	5
Rash	1	0	1

Other Toxicities	Grade 3	Grade 4	
Vomiting	7	0	
Nausea	5	0	
Infection	5	1	
Febrile Neutropenia	4	0	
Hypokalemia	2	3	
Hemoglobin	0	3	
Hemorrhage	2	0	

One episode of grade 3 toxicity each reported for elevated SGOT, renal insufficiency, dehydration, acidosis, seizure, somnolence, syncope, hematemesis, lymphopenia, bilirubin