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Rituximab and CHOP Chemotherapy Plus GM-CSF for Previously Untreated Diffuse Large B-Cell Lymphoma in the Elderly: A Wisconsin Oncology Network Study

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Abstract

Purpose—Human recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) may potentiate rituximab activity by upregulating CD20 expression and activating effector cells necessary for antibody-dependent cellular cytotoxicity. GM-CSF was combined with standard rituximab + CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) chemotherapy (R-CHOP) in the treatment of elderly patients with de novo diffuse large B-cell lymphoma (DLBCL).

Patients and Methods—Thirty-eight patients over the age of 60 years with newly diagnosed DLBCL were treated with R-CHOP every 21 days for 6–8 cycles and GM-CSF 250 µg/m² per day on days 3–10. Patients were evaluated for response after cycles 4, 6, and 8. The primary endpoint was the rate of complete response, and secondary endpoints were progression-free survival (PFS), event-free survival, and overall survival (OS).

Results—Thirty-eight patients were enrolled, with a median age of 72 years, and 29% of patients having high-risk disease (International Prognostic Index [IPI] score ≥ 4). A complete or unconfirmed complete response (CR) was achieved in 53% of patients. After a median follow-up of 51.1 months, the 3-year PFS and OS were 78% and 84%. Twenty-one percent of patients

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Author Contributions

Julie Chang collected and analyzed data and prepared the manuscript. Songwong Seo analyzed data and assisted with the manuscript preparation. Kyungmann Kim analyzed data and assisted with the manuscript preparation. Jae Werndli designed the trial and its implementation, and managed the data. Wayne Bottner designed the trial and its implementation. Gilberto Rodrigues designed the trial and its implementation. Federico Sanchez designed the trial and its implementation. Thomas Saphner designed the trial and its implementation. Walter Longo designed the trial and its implementation. Brad Kahl designed and performed research, assisted with the data analysis, and assisted with the manuscript preparation.

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discontinued protocol treatment because of chemotherapy-related toxicity and 16% because of GM-CSF toxicity. Dose intensity for planned chemotherapy cycles was 81.1%.

Conclusion—These data suggest that survival outcomes may be modestly improved when GM-CSF is combined with R-CHOP in the treatment of elderly DLBCL. GM-CSF had toxicity precluding planned administration in 16% of patients, which may limit usefulness of this agent. Further investigation of GM-CSF in combination with rituximab-containing chemotherapy is warranted.

Keywords

DLBCL; Granulocyte-macrophage colony-stimulating factor; Sargramostim; Toxicity

Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive subtype of non-Hodgkin lymphoma (NHL) that requires combination chemotherapy to achieve disease remission and long-term survival.¹ Previous studies have firmly established rituximab plus CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone; R-CHOP) chemotherapy as the standard therapy for patients with DLBCL, including elderly populations.^{2–7} Because half of the patients with newly diagnosed DLBCL are older than age 60 years at diagnosis, treatment in this older population is frequently complicated by the increased risk for chemotherapy-related toxicity and the presence of additional comorbidities.^{8,9} GM-CSF and other growth factors may improve chemotherapy tolerability by limiting chemotherapy-induced myelosuppression.^{10,11} Additional data suggests that GM-CSF may potentiate the activity of rituximab through upregulation of CD20 expression on tumor cells, stimulation of immune effector cells, and enhancement of rituximab-induced apoptosis.^{12–17} This study was undertaken to evaluate the tolerability and efficacy of GM-CSF combined with standard R-CHOP in an elderly population of patients with newly diagnosed DLBCL.

Patients and Methods

Patients

The study was approved by the Human Subjects Committee at the University of Wisconsin and by the Institutional Review Board at each participating Wisconsin Oncology Network institution. All patients signed an informed consent document describing the investigational nature of the proposed treatments.

Patients were eligible for this trial if they were older than 60 years of age with histologically confirmed CD20⁺ diffuse large B-cell lymphoma. Previous treatment was exclusionary with the exception of 1 cycle of CHOP or R-CHOP chemotherapy. Patients were required to have measurable or evaluable disease, have a baseline ECOG performance status of no greater than 2, and have no known evidence of central nervous involvement by lymphoma. Minimal laboratory requirements included a neutrophil count 1500/mm³, platelets 100,000/mm³, serum creatinine 2.0 mg/dL, serum bilirubin 1.5 mg/dL, and AST 2.5 times the laboratory upper limit of normal. Low blood counts were not exclusionary if related to splenomegaly or disease replacement of bone marrow. Abnormalities in hepatic and renal function were not exclusionary if related to tumor involvement of the organ. Patients were excluded if they were known to have an active second malignancy requiring radiation or chemotherapy treatments, HIV infection, chronic or active hepatitis B infection, any clinically significant and uncontrolled infection, or cardiac dysfunction (eg, New York Heart Association class III or IV disease or left ventricular ejection fraction < 45%).

Treatment

Patients were treated with rituximab 375 mg/m² intravenously (I.V.), cyclophosphamide 750 mg/m² I.V., doxorubicin 50 mg/m² I.V., vincristine 2 mg I.V., and prednisone 100 mg/m² orally on days 1–5 of each 21-day cycle. Sargramostim (granulocyte-macrophage colony-stimulating factor [GM-CSF]) was administered subcutaneously at a dose of 250 µg/m² per day on days 3–10 of each cycle. Antiemetic premedications were administered as per the institutional standard. All supportive measures were permitted throughout treatment including transfusion support and antibiotics. Patients received appropriate pneumocystis carinii pneumonia (PCP) prophylaxis with trimethoprim/sulfamethoxazole or dapsone.

Dose modifications for toxicity were specified in the protocol. A treatment cycle was defined as 21 days, with a maximum of 6–8 cycles of therapy. Protocol therapy was discontinued in the event of unacceptable toxicity, disease progression, or patient and/or physician discretion. Restaging computed tomography (CT) scans were performed after cycles 4, 6, and 8.

Criteria for Response

Patients were considered evaluable for response if they had completed at least 4 cycles of therapy and undergone an initial response evaluation by CT imaging or had completed at least 1 cycle of therapy and demonstrated disease progression before the first scheduled disease assessment. Patients were considered evaluable for toxicity if they had completed at least 1 cycle of therapy. Responses were defined by the International Working Group criteria.¹⁸

Statistical Considerations

The primary endpoint of this study was the observed rate of CR. A 2-stage design was undertaken to test the null hypothesis that a true CR rate is at most 45% versus the alternative hypothesis that it is at least 65%. The significance level of this test is 0.094 with a power of 85.4%. Initially, 18 evaluable patients were to be assessed for response, with plans to terminate enrollment early if there were 8 or fewer CR observed. An additional 17 evaluable patients were to be enrolled if there were 9 or more CR observed in the first stage of the study.

Secondary endpoints included determination of progression-free (PFS), event-free survival (EFS), and overall survival (OS), and assessment of tolerability and toxicity associated with the treatment. Progression-free survival was calculated from the date of enrollment until progression of disease or death from non-Hodgkin lymphoma. Event-free survival was defined as the time from enrollment until discontinuation of protocol therapy for any reason, progression, or death from any cause. Overall survival was calculated from the date of enrollment until death from any cause.

The overall complete and unconfirmed complete response rate (CR/CRu) with a corresponding 95% confidence interval (CI) was calculated using the exact binomial distribution, and the Kaplan-Meier (product-limit) method was used to estimate the survival functions for PFS, EFS, and OS. All statistical analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC) and Kaplan-Meier plots were created using R 2.5 software.

Results

Patients

Thirty eight patients from 6 institutions were entered into this study between April 20, 2002 and October 17, 2005. The baseline patient characteristics are summarized in Table 1. The median age for enrolled patients was 72, and almost one third of patients had high-risk disease with an International Prognostic Index (IPI) score of ≥ 4 .¹⁹ Less than 10% of patients had low-risk disease as defined by an IPI score of ≤ 1 .

Responses

Of the 38 enrolled patients, all were evaluable for toxicity and 29 were evaluable for response. Three patients did not complete 1 full cycle of protocol therapy (2 because of GM-CSF intolerance and 1 because of declining performance status), and were unevaluable for response. Six additional patients completed < 3 cycles of protocol therapy and were unevaluable for response.

During the first stage of planned enrollment, 21 patients were evaluated with 18 patients evaluable for response. Eleven of these 18 evaluable patients demonstrated evidence of CR/CRu. An additional 17 patients were then enrolled according to the 2-stage design with 9 additional CR/CRu responses observed. A CR/CRu was achieved in 53% (95% CI, 36%–69%) of enrolled patients (Table 2).

Survival

Twelve deaths have been observed after a median follow-up of 51.1 months. Eight deaths were related to progressive lymphoma and 4 deaths were observed from cardiovascular causes unrelated to lymphoma. All patients were included in the survival measures according to intention-to-treat analysis.

The 3-year PFS and OS were 78% (95% CI, 60%–88%) and 84% (95% CI, 68%–93%). The 5-year estimates for PFS and OS were 68% (95% CI, 50%–81%) and 70% (95% CI, 52%–82%). Three- and 5-year survival outcomes are shown in Figures 1–3. The median OS was 5.5 years. The 3-year EFS was 47% (95% CI, 31%–62%). The disparity between EFS and PFS is related to patients discontinuing protocol therapy because of intolerance issues in the absence of relapse.

Tolerability

Twenty-three patients (61%) completed the protocol treatment. Of the 15 patients not completing the protocol therapy, 1 patient died of complications of a stroke after cycle 3 of treatment and the remaining 14 patients discontinued therapy early as a result of toxicity (Table 3). Six patients (16%) discontinued protocol therapy because of GM-CSF intolerance and 8 patients (21%) discontinued the protocol therapy as a result of toxicity related to R-CHOP chemotherapy. Toxicity attributable to R-CHOP was observed as generalized decline in performance status in 5 patients and persistent cytopenias with inadequate marrow recovery in 3 patients. The majority of GM-CSF toxicities that resulted in discontinuation of treatment consisted of myalgias and arthralgias or local injection site reactions.

Five of the 6 patients who discontinued protocol therapy because of GM-CSF intolerance were able to complete 6–8 cycles of standard R-CHOP chemotherapy off-protocol. In comparison, none of the 8 patients discontinuing protocol therapy as a result of R-CHOP toxicity were able to receive a full course of treatment off-protocol. Dose intensity was calculated from the total cycles administered versus the total number of planned cycles.

Overall, 81.1% of planned therapy cycles were administered. Among the 15 patients unable to complete the protocol therapy, 48.3% of planned therapy cycles were administered.

Toxicity

The observed grade 3–5 observed toxicities (Table 4) were primarily related to toxicity from CHOP chemotherapy, with hematologic toxicities representing the most frequently observed toxicities. Although grade 3–4 events of leukopenia and neutropenia were frequently observed, there were no events of grade > 3 infectious complications observed and no deaths related to infectious complications. Frequent occurrences of grade 3 neurosensory and neuromotor complication were likely related to vincristine therapy. There was 1 event of tumor lysis syndrome with initiation of chemotherapy resulting in acute renal failure and need for a brief course of hemodialysis, with subsequent full recovery of renal function. One patient suffered a myocardial infarction and another patient suffered a fatal stroke during protocol therapy. Both patients were receiving GM-CSF at the time their thrombotic complications occurred and had pre-existing, extensive vascular disease.

Discussion

Advanced age remains the most important predictor for outcome in DLBCL as defined by the IPI.^{19,20} The poorer outcomes observed in adults over the age of 60 years may be related to several factors, including inherently more chemotherapy-resistant disease and/or the inability to tolerate multiagent chemotherapy because of other comorbidities. Multiple previous studies in older populations with DLBCL have shown inferior outcomes in terms of rates of complete remission and long-term survival when decreased doses of chemotherapy drugs were administered to these populations in order to improve tolerability and minimize drug toxicity.^{21–25} Rituximab has resulted in improved rates of remission and survival in all patients with DLBCL, and R-CHOP chemotherapy has been demonstrated to be the standard of care in 3 separate trials comparing CHOP with R-CHOP in the elderly population.^{2–6}

Rituximab has multiple in vivo mechanisms including complement-mediated lysis, antibody-dependent cytotoxicity, and induction of apoptosis. The primary mechanism by which rituximab exerts its anti-lymphoma effect remains undefined.^{17,26} GM-CSF has been observed in vitro to possibly potentiate rituximab activity by upregulation of CD20 expression on tumor cells and by stimulation of immune effector cells. Interferon α , IL-2, IL-4, IL-6, G-CSF, and GM-CSF have all been shown to enhance CD20 expression to variable degrees and also enhance rituximab binding to tumor cells.^{13,14,27} GM-CSF exposure was also observed to enhance rituximab-induced apoptosis of B-cell lymphoma cells.^{15–17} Previous phase II experience with GM-CSF plus rituximab in rituximab-naïve patients with relapsed follicular NHL suggested objective response rates that were higher than those predicted with rituximab alone.^{28,29} Based on these data, we hypothesized that GM-CSF administered in combination with R-CHOP would potentiate the activity of rituximab while facilitating the maintenance of dose intensity.

The outcomes in the current study compare favorably to those reported in the US intergroup and the GELA (Groupe d'Etude des Lymphomes de l'Adulte) trials, which tested R-CHOP chemotherapy in similar patient populations.^{2–5} With comparable follow-up, the GELA reported 5-year PFS and OS of 54% and 58%, compared with 68% and 70% observed in our trial. Comparison with the US intergroup experience is less straightforward, as those investigators used failure-free survival (which is defined differently than PFS). However, the US intergroup reported 3-year OS of 67%, compared with our 3-year OS of 84%.

Based on our experience, further investigation of GM-CSF combined with standard chemotherapy is warranted. Additional experience with GM-CSF raises questions as to

whether GM-CSF could be administered in a more optimal dosing schedule to further improve efficacy. For example, in the recent report by Cartron et al suggesting improved activity of GM-CSF plus rituximab compared with rituximab alone in relapsed follicular lymphoma, GM-CSF was administered on days 1–8 and rituximab on day 5 of each 21-day cycle.¹² It is possible that the efficacy from the combination of GM-CSF with rituximab is best achieved by “priming” of the immune response for several days before exposure of lymphoma cells to rituximab. The toxicity from the GM-CSF was not trivial, with 6 patients (16%) discontinuing as a result of toxicity that was clearly GM-CSF related and 2 additional patients discontinuing because of thrombotic events that may have been related. Previous studies have suggested an increased risk of thrombosis with GM-CSF usage.^{29,30}

Our clinical experience clearly demonstrates the ongoing challenges with chemotherapy toxicity in older populations, as 39% of enrolled patients were unable to complete the protocol therapy, mainly because of chemotherapy toxicity (21%) with subsequent inability to receive additional chemotherapy off-protocol. These issues with tolerability may be reflective of the enrolled population, with 29% of patients having high-risk disease by IPI criteria. By comparison, in the RICOVER-60 and GELA trials, < 20% of older adult DLBCL patients treated with R-CHOP chemotherapy had high-risk disease by IPI criteria, and both studies reported > 90% dose intensity for all cycles of chemotherapy.^{4–6} In contrast, the US intergroup included 28% IPI high-risk patients, and 20% of patients were unable to complete more than 5 cycles of induction chemotherapy.^{2,3}

Despite the fact that 9 out of 39 patients could not complete the planned R-CHOP chemotherapy, the outcome of our cohort was surprisingly good. We observed just 11 lymphoma relapses and 8 deaths from lymphoma, despite the advanced age and unfavorable IPI risk distribution. The vast majority of patients completing 6–8 cycles of R-CHOP chemotherapy were cured. This suggests that the relatively poor outcomes observed in older patients with DLBCL are more likely because of patients’ inability to tolerate curative therapy rather than affliction with a biologically more chemotherapy-resistant disease.

Conclusion

Diffuse large B-cell lymphoma in elderly patients remains a significant challenge given the aggressive nature of this disease, requiring multiagent chemotherapy to achieve long-term disease control, and the presence of multiple comorbidities in this population. These data support a beneficial effect of administering GM-CSF with standard R-CHOP chemotherapy in elderly patients with DLBCL, although further investigation is needed to prove the efficacy of GM-CSF in combination with R-CHOP chemotherapy. Future therapies directed at improving outcomes in elderly DLBCL will require significant emphasis on minimizing toxicities.

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Figure 1.
Kaplan-Meier Plots of Overall Survival (n = 38)

Figure 2.
Kaplan-Meier Plot of Progression-Free Survival (n = 38)

Figure 3.
Kaplan-Meier Plot of Event-Free Survival (n = 38)

Table 1

Baseline Characteristics of Study Participants (n = 38)

Characteristic	Number	Percent
Evaluable for Response	29	76
Sex		
Male	22	58
Female	16	42
Age (at on-Study)		
Median	72	–
Range	62–86	–
Performance Status		
0	10	26
1	18	47
2	10	26
International Prognostic Index		
0–1	3	8
2–3	24	63
4–5	11	29
Stage		
I–II	6	16
III	12	32
IV	20	53
Elevated LDH		
Yes	21	55
No	17	45
B Symptoms		
Yes	21	55
No	17	45
Number Extranodal Sites		
0	13	34
1	16	42
2	9	24

Abbreviation: LDH = lactate dehydrogenase

Table 2

Response Rates to Protocol Therapy (n = 38)

Response Measure	Number	Percent
Complete Response	11	29
Unconfirmed Complete Response	9	24
Partial Response	9	24
Stable Disease	0	0
Progressive Disease	0	0
Unevaluable	9	24

Table 3

Reasons for Early Discontinuation of Therapy

Reason	Number	Percent
Discontinued Protocol Therapy	15	39
Death Unrelated to Lymphoma	1	3
Toxicity	14	37
R-CHOP Toxicity	8	21
Declining Performance Status	5	13
Persistent Cytopenias	3	8
GM-CSF Toxicity	6	16

Abbreviations: GM-CSF = granulocyte-macrophage colony-stimulating factor; R-CHOP = rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone

Table 4

Worst Grade 3–5 Toxicity Event per Patient (n = 38)

Toxicity	Grade 3	Grade 4	Grade 5
Hematologic			
Leukopenia	12	11	0
Neutropenia	5	16	0
Thrombocytopenia	9	3	0
Hemoglobin	8	2	0
Thrombosis	1	0	0
Infectious			
Infection with Neutropenia	7	0	0
Infection without Neutropenia	4	0	0
Febrile Neutropenia	2	0	0
Constitutional/Metabolic			
Fatigue	3	0	0
Pain	3	0	0
Anorexia	1	0	0
Hyperglycemia	2	1	0
Hyponatremia	1	0	0
Hypocalcemia	0	1	0
Tumor lysis syndrome	1	0	0
Cytokine release syndrome	1	0	0
Renal failure	1	0	0
Cardiovascular			
Dyspnea	2	0	0
Hypotension	1	0	0
Myocardial Infarction	0	1	0
Stroke	0	0	1
Left ventricular dysfunction	1	0	0
Gastrointestinal			
Nausea	4	0	0
Vomiting	2	0	0
Mucositis	1	0	0
Constipation	1	0	0
GI Bleeding	1	1	0
Epigastric Pain	2	0	0
Small bowel obstruction	0	1	0
Neurologic			
Neurosensory	6	0	0
Neuromotor	4	0	0

Toxicity	Grade 3	Grade 4	Grade 5
Syncope	1	0	0
Hallucinations	2	0	0
Musculoskeletal			
Myalgias/arthralgias	2 ^a	0	0

^aIncludes 1 patient who required discontinuation of GM-CSF for symptoms.

Abbreviations: GI = gastrointestinal; GM-CSF = granulocyte-macrophage colony-stimulating factor