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Serious pulmonary toxicity in patients with Hodgkin's lymphoma with SGN-30, gemcitabine, vinorelbine, and liposomal doxorubicin is associated with an FcγRIIIa-158 V/F polymorphism

K. A. Blum[1]*, S.-H. Jung[2], J. L. Johnson[2], T. S. Lin[1], E. D. Hsi[3], D. M. Lucas[1], J. C. Byrd[1], B. D. Cheson[4] & N. L. Bartlett[5] for the Cancer and Leukemia Group B

[1]Division of Hematology–Oncology, The Ohio State University Medical Center, Columbus, OH; [2]CALGB Statistical Center, Duke University Medical Center, Durham, NC; [3]Department of Clinical Pathology, Cleveland Clinic, Cleveland, OH; [4]Division of Hematology–Oncology, Georgetown University Hospital, Washington, DC; [5]Division of Hematology–Oncology, Washington University School of Medicine, St Louis, MO, USA

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Background: Based on *in vitro* synergistic cytotoxicity when anti-CD30 antibodies are combined with gemcitabine, the Cancer and Leukemia Group B conducted a double-blind, randomized, phase II trial of SGN-30 with gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD) in patients with relapsed Hodgkin's lymphoma.
Patients and methods: In part 1 of the trial, 16 patients received SGN-30 with GVD to assess the safety of the combination. In part 2, patients were randomly allocated to SGN-30 ($n = 7$) or placebo ($n = 7$) with GVD to determine overall response rate (ORR).
Results: ORR in all 30 patients was 63% (65% with SGN-30 plus GVD, $n = 23$, and 57% with placebo plus GVD, $n = 7$). Median event-free survival was 9.0 months, with no difference between the two arms. Grades 3–5 pneumonitis occurred in five patients receiving SGN-30 and GVD, leading to premature closure of the trial. All five patients with pulmonary toxicity had a V/F polymorphism in the FcγRIIIa gene ($P = 0.008$).
Conclusions: Together with historical data demonstrating a 2% incidence of pulmonary events with GVD, these results indicate that SGN-30 cannot safely be administered concurrently. The risk of pneumonitis with SGN-30 and GVD is greatest in patients with an FcγRIIIa V/F polymorphism.
Key words: classical Hodgkin's lymphoma, FcγRIIIa polymorphism, gemcitabine, pneumonitis, SGN-30

introduction

CD30 is an ideal target for antibody therapy in Hodgkin's lymphoma (HL) since CD30 expression can be detected on Reed-Sternberg cells in 84%–91% of classical HL specimens and is otherwise absent on normal tissue with the exception of activated B and T cells [1–3]. SGN-30 is a chimeric anti-CD30 monoclonal antibody construct with activity in SCID mouse xenograft models of HL, with treatment resulting in a dose-dependent reduction in tumor mass and prolonged survival [4]. In phase I testing of single-agent SGN-30, no dose-limiting toxic effects were observed and activity in relapsed HL was modest with one partial response (PR) and stable disease (SD) in four patients for 6–16 months ($n = 34$) [5].

Preclinical data with anti-CD30 antibodies indicate that synergistic cytotoxic effects can be observed when combined with gemcitabine in HL cell lines [6, 7]. In a previous Cancer and Leukemia Group B (CALGB) trial, combination therapy with gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD) had significant efficacy as pretransplant salvage therapy and in patients relapsed after stem cell transplant (SCT), with an overall response rate (ORR) of 70% [8]. Grades 3–4 toxic effects consisted primarily of myelosuppression and mucositis. Less common events included transaminitis ($n = 5$), dyspnea ($n = 4$), pneumonitis ($n = 1$), and acute respiratory distress syndrome ($n = 1$).

On the basis of the synergistic efficacy of anti-CD30 antibodies and gemcitabine *in vitro* and *in vivo* [6] and the significant activity of GVD [6–8], the CALGB initiated a double-blind, randomized, phase II trial of SGN-30 or placebo with GVD in patients with relapsed or refractory classical HL as pre- and post-transplant salvage therapy to determine overall ORR and event-free survival (EFS).

*Correspondence to: Dr K. A. Blum, Division of Hematology–Oncology, Arthur G. James Comprehensive Cancer Center, The Ohio State University, B315 Starling Loving Hall, 320 W 10th Ave, Columbus, OH 43210, USA. Tel: +1 (614) 293-8858; Fax: +1 (614) 293-7484; E-mail: kristie.blum@osumc.edu

Secondary objectives included assessment of SGN-30 pharmacokinetics, human anti-chimeric antibody (HACA) formation, soluble CD30 (sCD30) levels, and Fc gamma (γ) receptor single nucleotide polymorphisms.

patients and methods

patient selection

Patients ≥18 years of age with histologically confirmed CD30+ classical HL relapsed or refractory after at least one prior therapy were enrolled. Previous treatment with an anti-CD30 antibody, gemcitabine, vinorelbine, or pegylated liposomal doxorubicin was not permitted. Candidates for SCT could receive two or more cycles of protocol therapy as salvage therapy before transplant. Additional inclusion criteria included Eastern Cooperative Oncology Group performance status of two or less, left ventricular ejection fraction ≥45%, measurable disease ≥1 cm, absolute neutrophil count (ANC) ≥1200/μl, platelet count ≥100 000/μl, creatinine ≤2.0 mg/dl, bilirubin ≤2.0 mg/dl, and aspartate aminotransferase ≤2.5 × the institutional upper limit of normal. The Institutional Review Board of each participating site approved the protocol, and all patients provided written informed consent according to the Declaration of Helsinki.

study design

From April 2006 to December 2007, 10 CALGB-affiliated institutions accrued patients to this trial. The trial was conducted in two parts. Part 1 was designed to confirm the safety of combination therapy with SGN-30 and GVD. After 16 patients completed at least one cycle of combined SGN-30 and GVD, part 2 was initiated to assess ORR. In part 2, patients were randomized to receive either SGN-30 or placebo with GVD. Patients, treating physicians, and the study chair were blinded to the use of SGN-30 or placebo. Biweekly telephone conference calls among the study chair, statistician, data coordinator, and treating physicians were carried out during parts 1 and 2 of the study to monitor adverse events.

drug formulation and administration

All patients in part 1 of the trial received 12 mg/kg of SGN-30 i.v. followed by GVD on days 1 and 8 of a 21-day treatment cycle (Table 1). In part 2, patients received either 12 mg/kg of SGN-30 or 12 mg/kg of placebo followed by GVD on days 1 and 8 (Table 1). SGN-30 was administered at a rate of 100 mg/h for 30 min. If no infusion reaction was observed, the remainder was infused over 90 min, for a total infusion time of 2 h. GVD was administered as previously described [8], with dosing dependent on whether the patient had a previous transplant (Table 1). Treatment was administered for a maximum of six cycles. Response was evaluated by computed tomography (CT) scan every two cycles and by positron emission tomography (PET) or PET/CT at completion of treatment according to International Harmonization Project Response Criteria [9]. Responding patients were permitted to stop protocol therapy after two or more cycles to undergo SCT.

On days 1 and 8, an ANC ≥ 1200/μl and platelets ≥ 75 000/μl and an ANC ≥ 1000/μl and platelets ≥ 50 000/μl, respectively, were required. Filgrastim was instituted on days 3–6 and 10–15 of each cycle for dose delays for neutropenia or for febrile neutropenia. Liposomal doxorubicin was dose reduced by 25% for grades 3–4 mucositis or hand–foot syndrome. Infusion reactions secondary to SGN-30 or pegylated liposomal doxorubicin were treated with diphenhydramine, acetaminophen, histamine blockade, and/or steroids. Protocol therapy was held for new or worsening cough, dyspnea, hypoxia, or pulmonary infiltrates.

Table 1. Part 1 and part 2 dosing schedules of SGN-30 plus GVD or placebo plus GVD in patients, dependent on prior stem cell transplantation

	Drug	Dose	Schedule
Part 1			
No prior transplant	SGN-30	12 mg/kg	D1 and D8 q21 days
	Gemcitabine	1000 mg/m^2	D1 and D8 q21 days
	Vinorelbine	20 mg/m^2	D1 and D8 q21 days
	Pegylated liposomal doxorubicin	15 mg/m^2	D1 and D8 q21 days
Prior transplant	SGN-30	12 mg/kg	D1 and D8 q21 days
	Gemcitabine	800 mg/m^2	D1 and D8 q21 days
	Vinorelbine	15 mg/m^2	D1 and D8 q21 days
	Pegylated liposomal doxorubicin	10 mg/m^2	D1 and D8 q21 days
Part 2			
No prior transplant	SGN-30 or placebo	12 mg/kg	D1 and D8 q21 days
	Gemcitabine	1000 mg/m^2	D1 and D8 q21 days
	Vinorelbine	20 mg/m^2	D1 and D8 q21 days
	Pegylated liposomal doxorubicin	15 mg/m^2	D1 and D8 q21 days
Prior transplant	SGN-30 or placebo	12 mg/kg	D1 and D8 q21 days
	Gemcitabine	800 mg/m^2	D1 and D8 q21 days
	Vinorelbine	15 mg/m^2	D1 and D8 q21 days
	Pegylated liposomal doxorubicin	10 mg/m^2	D1 and D8 q21 days

GVD, gemcitabine, vinorelbine, and pegylated liposomal doxorubicin.

SGN-30 pharmacokinetics, HACA, sCD30 antigen, and Fcγ receptor polymorphism detection

Sample submission for SGN-30 pharmacokinetics, sCD30 levels, HACA, and Fcγ receptor polymorphisms was optional. Blood samples were collected immediately before treatment on cycle 1 of day 1 and within 1 h after the last SGN-30/placebo infusion. Serum was separated and stored at −20°C until assayed at a central laboratory (Covance, Princeton, NJ). A validated enzyme-linked immunosorbent sandwich assay method was used to measure SGN-30 pharmacokinetics, HACA responses, and sCD30 levels according to THE published methods [5]. The Fcγ receptor polymorphism analyses were carried out as previously described [10], with minor modifications to PCR conditions. Primers were obtained from Integrated DNA Technologies (Coralville, IA). PCR was carried out using HotStar Taq Master Mix (Qiagen, Valencia, CA) on an iCycler instrument (BioRad, Hercules, CA). Restriction enzymes were obtained from New England Biolabs (Ipswich, MA) and products were resolved by polyacrylamide gel electrophoresis.

statistical analysis

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by review of data by the CALGB Statistical Center and study chair. As part of the CALGB quality assurance program, members of the Audit Committee visit all participating institutions at least once every 3 years to verify compliance with federal regulations and protocol requirements, including eligibility, treatment,

adverse events, response, and outcome. Such on-site review of medical records was carried out for 2 (7%) of the 30 participants in this study.

Part 1 of this trial was designed to confirm the safety of combination therapy of GVD and SGN-30, with plans to stop the study for revision if grades 3–4 nonhematologic events were observed in 7 or more of the 16 patients during cycle 1 of SGN-30 and GVD. This rule has a 50% of stopping probability if the true probability of grades 3–4 nonhematologic toxicity was 40% in cycle 1. Part 2 was a randomized, double-blind, placebo controlled trial designed to evaluate the ORR of SGN-30 plus GVD and placebo plus GVD. Randomization to each treatment arm was stratified according to previous SCT (no, yes). Based on previous data with GVD [8], a two-stage study with a 0.80 power and 0.16 type I error rate was used to test the hypothesis that the ORR with SGN-30 and GVD was 85% and the ORR with placebo and GVD was 70%. In stage 1 of the study, 27 patients were planned for each arm, with an additional 36 patients enrolled per arm in stage 2, for a total of 126 patients.

After unexpected pulmonary toxicity was observed in two patients on part 1, part 2 was amended to require study closure if a 20% excess risk of grade 2 or higher was observed with SGN-30 compared with placebo. Four interim evaluations of toxicity data were planned and study closure required if ≥2 in 10 patients, ≥2 in 20 patients, ≥3 in 30 patients, and ≥4 in 40 patients experienced grade 2 or higher pulmonary events with SGN-30 compared with the placebo. Unblinding of patient's treatment arm occurred for grades 4–5 pulmonary toxicity and when interim toxicity evaluation resulted in study closure.

The Kaplan–Meier method was used to estimate EFS measured from the time of trial entry until progression, death, or termination of treatment due to nonresponse and overall survival (OS) measured from trial entry until death. Patients who went on to receive an SCT were not censored from the EFS survival at the time of transplant and were only considered failures at the time of relapse or death from any cause. Toxicity was reported according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Fisher's exact test was used to correlate Fcγ receptor polymorphisms with response, although statistical analysis of the correlative study data was exploratory due to the small sample size. The log-rank test was used to compare EFS and OS data according to treatment arm and previous transplant stratification. The median test was used to determine the association of SGN-30 pharmacokinetics and sCD30 levels with response and toxicity.

results

patient characteristics

Sixteen patients treated with SGN-30 and GVD in part 1 and 14 patients randomly allocated to SGN-30 and GVD ($n = 7$) or placebo and GVD ($n = 7$) in part 2 were evaluable for response and toxicity. A diagnosis of classical HL was confirmed by central review in 23 patients (nodular sclerosis subtype, $n = 19$; mixed cellularity, $n = 2$; and unclassifiable, $n = 2$). Pathological samples were necrotic in three patients and not provided for central review in four patients. Patient characteristics are detailed in Table 2. There were no statistically significant differences in patient characteristics by treatment arm (Table 2) or in transplant naive ($n = 19$) compared with previously transplanted patients ($n = 11$), with the exception of the number of prior therapies (data not shown). The median time to study entry from autologous transplant in the 11 patients who were previously transplanted was 9 months (range 4–69 months). Sites of previous irradiation included the mediastinum or mantle field in nine patients, thoracic and lumbar spine in two patients, and pelvis in one patient.

treatment, response, and survival

Patients completed a median of three cycles (range 1–6) of SGN-30 or placebo and GVD. Nineteen patients responded (ORR 63%), with 10 complete response (CR) and 9 PR by CT and PET/CT using International Harmonization Response Criteria [9]. Thirteen patients, including 8 patients with a CR and 2 patients with a PR, stopped protocol therapy after two or more cycles to undergo SCT (9 autologous and 4 allogeneic). No significant differences were observed in ORR by treatment arm, with an ORR of 65% in 23 patients receiving SGN-30 and GVD and 57% in 7 patients receiving placebo and GVD. Responses were also similar in transplant naive patients (ORR 63%) and previously transplanted patients (ORR 64%).

With a median follow-up of 12 months (range 4–21 months), the median EFS was 9.0 months (Figure 1A) and the median OS has not yet been reached. Figures 1B and C demonstrate no significant differences in EFS in patients receiving SGN-30 or placebo and in transplant naive patients compared with previously transplanted patients, respectively. The median EFS in the SGN-30 and GVD arm was 11.3 months and in the placebo and GVD arm was 4.1 months. The median EFS was 7.8 and 15.6 months in the previously transplanted and transplant naive patients, respectively. With six deaths due to treatment-related toxicity ($n = 2$) and disease progression ($n = 4$), the estimated probability of survival at 1 year is 78% (95% confidence interval 0.53–0.98).

adverse events

Grades 3–4 hematologic toxicity consisted of neutropenia (60%), anemia (37%), and thrombocytopenia (26%, Table 3). Forty percent of patients required filgrastim. Febrile neutropenia occurred in 13% of patients. Nonhematologic events included fatigue, nausea, vomiting, mucositis, rash, hand–foot syndrome, and reversible transaminitis (Table 3). Two patients experienced infusion reactions with liposomal doxorubicin but were able to tolerate subsequent infusions with premedication and slower infusion rates. No reactions were observed with SGN-30 administration.

Five patients experienced grades 3–5 pulmonary toxicity (Table 4). Two patients in part 1 were intubated for fever, hypoxia, and bilateral pulmonary infiltrates after two to three cycles of SGN-30 and GVD. In both patients, bronchoalveolar lavage demonstrated no evidence of acid-fast bacilli, *Pneumocystis*, *Legionella*, or other bacterial, fungal, or viral pathogens. One of these two patients died despite treatment with broad-spectrum antimicrobials and high-dose methylprednisolone, and the other patient eventually recovered without steroids. In the randomized trial, three patients had grades 3–5 pneumonitis after two to five cycles of SGN-30 and GVD. Bronchoalveolar lavage cultures in two of the three patients were negative, transbronchial biopsy demonstrated no evidence of HL, and these two patients improved with antibiotics and high-dose steroids. In the third patient, autopsy demonstrated hemorrhagic cavitation in the left lower and right upper lobes without HL, and post-mortem cultures grew *Pseudomonas aeruginosa* and *Enterococcus* despite adequate antibiotic coverage for both organisms. No grade 2 or higher pulmonary adverse events were observed in the placebo arm.

Table 2. Patient demographics by treatment arm

Characteristic	All patients ($n = 30$), n (%)	SGN-30 + GVD ($n = 23$), n (%)	Placebo + GVD ($n = 7$), n (%)	P value
Median age (range), years	35 (19–78)	35 (19–78)	38 (25–53)	0.94
Male : female	23 : 7	18 : 5	5 : 2	1.00
Number of prior therapies (range)	2 (1–4)	1 (1–4)	2 (1–2)	0.93
Prior autologous transplant	11 (37)	8 (35)	3 (42)	1.00
Refractory to last therapy	12 (41)	9 (39)	3 (42)	1.00
Stage				
II	8 (27)	7 (30)	1 (14)	0.68
III	3 (10)	2 (9)	1 (14)	
IV	19 (63)	14 (61)	5 (71)	
B-symptoms	8 (28)	6 (27)	2 (29)	1.00
Eastern Cooperative Oncology Group performance status				
0–1	23 (77)	18 (78)	5 (71)	
2	7 (23)	5 (22)	2 (29)	1.00
Initial therapy				
ABVD[a]	26 (87)	19 (83)	7 (100)	
Doxorubicin/bleomycin	1 (3)	1 (4)	0	
MOPP/ABV[a]	1 (3)	1 (4)	0	
Stanford V[a]	2 (7)	2 (9)	0	
Second-line therapy				
None	15 (50)	12 (52)	3 (43)	
ICE/DICE[a]	9 (30)	7 (30)	2 (29)	
ESHAP[a]	3 (10)	2 (9)	1 (14)	
MOPP[a]	2 (7)	1 (4)	1 (14)	
ABVD[a]	1 (3)	1 (4)	0	
Prior radiation	12 (40)	9 (39)	3 (43)	1.00

GVD, gemcitabine, vinorelbine, and pegylated liposomal doxorubicin.

[a]ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; MOPP/ABV: nitrogen mustard, vincristine, prednisone, procarbazine, doxorubicin, bleomycin, vinblastine; Stanford V: doxorubicin, vinblastine, vincristine, bleomycin, nitrogen mustard, etoposide, prednisone; ICE: ifosfamide, carboplatin, etoposide; DICE: dexamethasone, ifosfamide, carboplatin, etoposide; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; MOPP: nitrogen mustard, vincristine, prednisone, procarbazine.

As a result, in accordance with part 2 study stopping rules, the trial was closed to accrual in December 2007, study therapy was unblinded, and SGN-30 was discontinued in all patients. The patient with *Pseudomonas* and *Enterococcal* pneumonia was included in the determination to close the trial as the patient had fatal pulmonary infiltrates with negative blood cultures, despite broad-spectrum antibiotics and high-dose steroids, and autopsy results were not immediately available. In univariate analysis, age, gender, number of prior therapies, time from last treatment, prior autologous SCT, prior radiation, use of filgrastim, and the number of GVD cycles were not significantly associated with the development of grades 3–5 pneumonitis (Ps = 0.34–1.00).

pharmacokinetics, sCD30, HACA, and Fcγ receptor polymorphisms

Peak SGN-30 levels in 10 patients were 141–565 μg/ml, with a median of 339 μg/ml. Two of these 10 patients developed grades 3–5 pulmonary adverse events, and their peak SGN-30 concentrations were 335 and 363 μg/ml, respectively. Peak SGN-30 concentration failed to correlate with response, with a median value of 343 μg/ml (range 189–365 μg/ml) in five responding patients compared with 353 μg/ml (range 141–565 μg/ml) in five nonresponding patients ($P = 0.27$).

The median pretreatment sCD30 level in nine patients was 76.5 U/ml (range 14.3–1992.0 U/ml). One of these nine patients developed pulmonary toxicity with sCD30 level of 57.0 U/ml. There was no correlation with pretreatment sCD30 level and response, with a median of 174.2 U/ml (range 14.3–1992.0 U/ml) in four responding patients compared with 76.5 U/ml (range 21–219.0 U/ml) in five nonresponding patients ($P = 0.06$). In 19 patients, HACA titers were not detected at the end of protocol therapy.

FcγRIIa and FcγRIIIa polymorphisms were assessed in 28 patients. No patients were homozygous for expression of valine (V/V) on FcγRIIIa-158, 16 patients were homozygous for phenylalanine (F/F), and 12 patients were heterozygous (V/F). All five patients with grades 3–5 pneumonitis had a V/F genotype (Table 5, $P = 0.008$). If the patient with pneumonia (patient 4 in Table 4) is not included, then 4 of the 12 patients with a V/F FcγRIIIa polymorphism developed grades 3–5 pneumonitis, which remains significant with a P value of 0.024. There was no significant difference in ORR, CR, or progression-free survival (PFS) rate in patients with F/F or V/F genotypes (Table 5). In contrast, genomic polymorphisms in

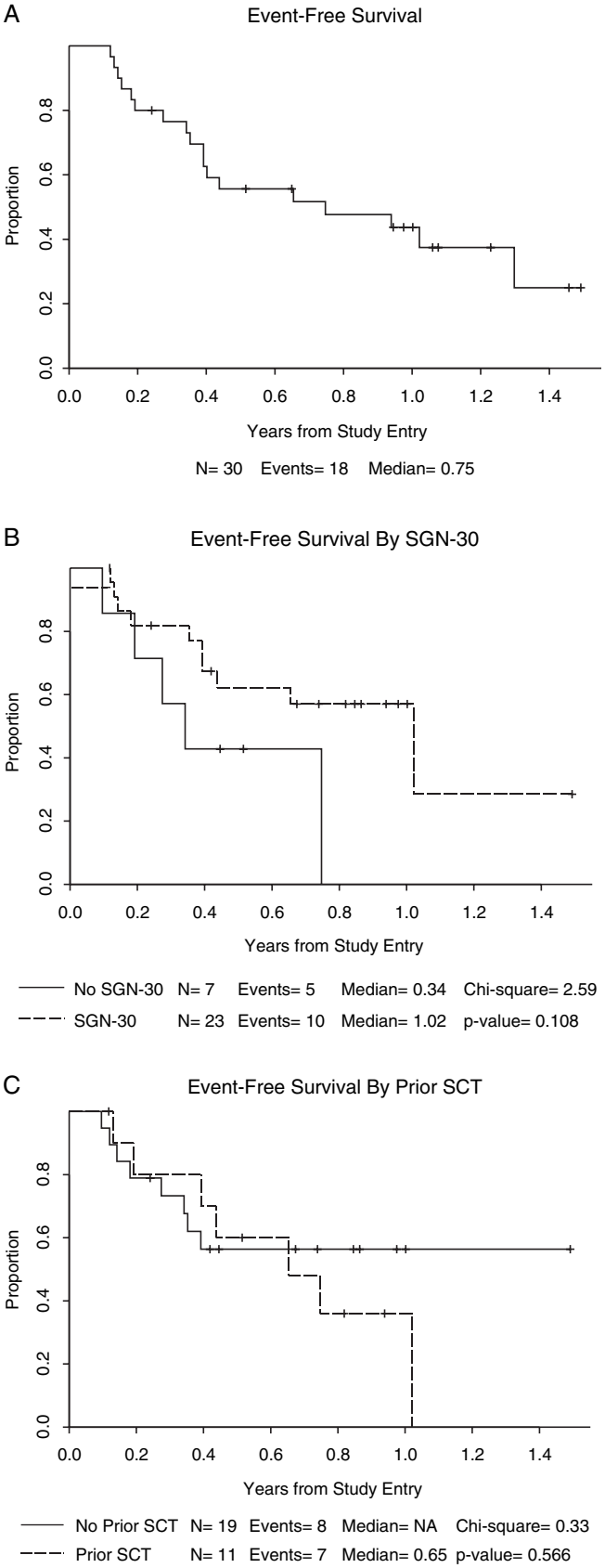

Figure 1. (A) Event-free survival (EFS) for all patients ($n = 30$) with relapsed or refractory classical Hodgkin's lymphoma (HL) receiving SGN-30 and gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD) and placebo and GVD. (B) EFS for patients with relapsed or refractory classical HL according to treatment arm: SGN-30 and GVD ($n = 23$, dashed line) or placebo and GVD ($n = 7$, solid line). (C) EFS for transplant naive ($n = 19$, solid line) patients and previously transplanted patients ($n = 11$, dashed line) with relapsed or refractory classical HL receiving SGN-30 and GVD and placebo and GVD.

FcγRIIa-131 correlated with outcome but not with pulmonary toxicity. Three patients were homozygous for expression of histidine (H/H), 8 patients were homozygous for arginine (R/R), and 17 patients were heterozygous (H/R). Higher ORR and CR were observed in patients with the R/R genotype (Table 5), and PFS significantly favored patients with either the R/R or the H/R genotypes (Figure 2).

discussion

This study was designed to determine the ORR and EFS with SGN-30 and GVD in patients with relapsed classical HL; however, unexpected grades 3–5 pneumonitis prevented study completion. Twenty-one percent (5 of 23) of patients receiving SGN-30 and GVD developed pneumonitis compared with 0 of the 7 patients receiving placebo and GVD and 2.2% (2 of 91) of patients treated with GVD in the previous CALGB trial [8]. Clinical features in all five patients with pneumonitis were similar with fever after two to five cycles of SGN-30 and GVD, followed by the rapid development of dyspnea, hypoxia, and bilateral pulmonary infiltrates. In four of the five patients, there was no evidence of infection or progressive HL. Age, gender, number of prior therapies, time from last treatment, prior autologous SCT, prior radiation, use of filgrastim, and the number of GVD cycles did not correlate with the development of pulmonary toxicity. Interestingly, all five patients with pneumonitis have the same V/F FcγRIIIa genotype, indicating that FcγRIIIa-158 may serve as a predictive marker for this unexpected toxicity.

The incidence of gemcitabine-related pulmonary toxicity is <1% [11]. Pneumonitis occurs more frequently in patients receiving concurrent gemcitabine and radiation [12, 13]. In patients with HL, symptomatic pneumonitis has also been observed when gemcitabine is combined with bleomycin [14, 15]. However, gemcitabine alone is unlikely to be the only etiology of pneumonitis in this trial as it has been safely administered as a single agent [16] and in combination [8, 17, 18] to heavily pretreated HL patients. Eight patients on the prior GVD trial developed grades 3–4 dyspnea, but in only two cases was this associated with pulmonary infiltrates [8]. Previous therapies including SCT or mediastinal radiation are also unlikely to have increased the risk for the pulmonary events in the current study, as only two of the five patients had previously received radiation and one patient had a prior transplant. Eight patients with previous mediastinal or mantle irradiation did not develop pulmonary infiltrates after either GVD alone ($n = 2$) or the combination ($n = 6$).

Therefore, we presume that the likely cause of pneumonitis is an interaction between SGN-30 and gemcitabine. In single-agent phases I–II trials with the anti-CD30 antibodies SGN-30

and MDX-060, grades 3–4 dyspnea has been reported in 0 of the 24 patients and 3 of the 72 patients, respectively. Interstitial pneumonitis has been reported with the anti-CD20 antibody, rituximab, although the incidence is quite low [19, 20]. Similar to our trial, dyspnea, fever, and diffuse ground glass opacities that can be fatal and not always responsive to steroids have been described [20]. Proinflammatory cytokine release including tumor necrosis factor-α, interferon-γ, interleukin (IL)-4, IL-6, and IL-8 has been postulated to contribute to rituximab-related lung disease [20] and may explain the pulmonary events observed in this trial. CD30 signaling is implicated in autoimmunity [21–27], and sCD30 is increased in a variety of fibrotic lung diseases, including scleroderma lung disease, posttransplant bronchiolitis obliterans, interstitial pulmonary fibrosis, and Wegener's granulomatosis [28–31]. Th2 cytokine expression and CD8+ T-cell infiltration characterize the inflammatory pulmonary infiltrates in these same diseases [31–35]. Macrophage-mediated antibody-dependent cellular phagocytosis is required for SGN-30 efficacy [36], and perhaps alveolar macrophage binding to SGN-30 in patients with the V/F FcyRIIIa polymorphism and consequent cytokine release ultimately exacerbated subclinical gemcitabine-induced pulmonary damage. Although previous studies of single-agent SGN-30 [5] and the GVD combination study did not evaluate Fcy receptor polymorphisms [8], it is unlikely that the V/F FcyRIIIa polymorphism alone is sufficient to cause pneumonitis as 7 of the 12 patients on this trial with the V/F FcyRIIIa polymorphism had no evidence of grades 3–4 pulmonary toxicity. However, further exploration of the contribution of CD8+ T cells, cytokine release, and alveolar macrophage proliferation and cellular killing will be needed to support these speculations.

In this study, the ORR and median EFS were 63% and 9.0 months, respectively. Outcomes were similar in the SGN-30 and placebo arms. Historical data with GVD also demonstrate an ORR of 70% [8]. Although the CR rate in the current trial reached 33% compared with 19% with GVD [8], this likely

Table 3. Adverse events

Toxicity	Grade		
	3 (%)	4 (%)	5 (%)
Hematologic			
Anemia	11 (37)		
Neutropenia	7 (23)	11 (37)	
Thrombocytopenia	4 (13)	4 (13)	
Lymphopenia	3 (10)	1 (3)	
Infection			
Febrile neutropenia	4 (13)		
Infection with normal ANC	3 (10)		1 (3)
Nonhematologic			
Fatigue	3 (10)		
Rash	2 (7)		
Hand–foot syndrome	2 (7)		
Mucositis	2 (7)		
Nausea/vomiting	3 (10)		
Transaminitis	3 (10)		
Doxil infusion reaction	2 (7)		
Cough	1 (3)		
Dyspnea	2 (7)		
Pneumonitis	2 (7)	1 (3)	1 (3)

ANC, absolute neutrophil count.

Table 4. Characteristics of patients with grades 2–5 pulmonary adverse events

Age	Gender	Prior therapy (months before study entry)	History of bleomycin toxicity	Number of SGN-30 cycles	Response to SGN-30 and GVD	Adverse event	Treatment	Bronchoscopy/autopsy findings
62	F	ABVD × 6 (2.5), radiation to T-spine (2)	N	Part 1, 2 cycles	PD	Gr. 5 Pneumonitis	Ceftazidime, vancomycin, fluconazole, methylprednisolone	Polymorphonuclear cells, rare *Candida albicans*
36	M	ABVD × 8 (7), ICE × 4 (2)	N	Part 1, 3 cycles	SD	Gr. 4 Pneumonitis	Broad-spectrum antibiotics	Negative cultures
39	M	ABVD × 6 (12), ICE × 2 (10), mediastinal radiation (8), autologous transplant (8)	N	Part 2, 2 cycles	CR	Gr. 3 Pneumonitis	Levofloxacin, high-dose steroids	Negative cultures and no evidence of HL on transbronchial biopsy
40	M	ABVD × 6 (16)	Y	Part 2, 5 cycles	SD	Gr. 5 pseudomonal/ enterococcal pneumonia	Broad-spectrum antibiotics, fluconazole, caspofungin, linezolid, methylprednisolone	Necrotizing enterococcal/ pseudomonal pneumonia, mild interstitial fibrosis, no HL
26	M	ABVD × 6 (10)	Y	Part 2, 4 cycles	PR	Gr. 3 Pneumonitis	Broad-spectrum antibiotics, high-dose steroids	CD3+ T cells, negative cultures, no evidence of HL on transbronchial biopsy

HL, Hodgkin's lymphoma; CR, complete response; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ICE, ifosfamide, carboplatin, and etoposide; PD, progressive disease; SD, stable disease; PR, partial response; Gr, grade.

Table 5. Response, PFS, and pulmonary toxicity according to patients' Fcγ receptor polymorphisms

FcγR polymorphism	Response		1-year PFS	Grades 3–5 pulmonary toxicity
	CR	OR		
FcγRIIa				
R/R	5/8 (63%)	7/8 (88%)	0.47 (95% CI 0.12–0.76)	1/8 (13%)
R/H	5/17 (29%)	10/17 (59%)	0.78 (95% CI 0.46–0.93)	2/17 (12%)
H/H	0/3 (0%)	0/3 (0%)	0.50 (95% CI 0.05–0.95)	2/3 (67%)
P value	0.110	0.029	0.004	0.117
FcγRIIIa				
F/F	6/16 (38%)	10/16 (63%)	0.67 (95% CI 0.38–0.85)	0/16 (0%)
F/V	4/12 (33%)	7/12 (58%)	0.53 (95% CI 0.15–0.81)	5/12 (42%)
P value	1.00	1.00	0.95	0.008

PFS, progression-free survival; CR, complete response; CI, confidence interval.

reflects the use of PET-assessed response. In previously transplanted patients, a median EFS of 8.5 months was reported with GVD alone [8], similar to the median EFS of 7.8 months seen on this trial. In transplant naive patients, median EFS was not reached (52% at 4 years) [8], improved over the median EFS of 15.6 months on the current trial; however, more patients on the current study had refractory disease (41% versus 16%) and fewer patients proceeded to SCT (53% versus 76%).

Our study indicates that low-affinity R/R or H/R polymorphisms in FcγRIIa are associated with improved response and EFS to SGN-30, opposite of what is observed with rituximab in follicular lymphoma, where the H/H genotype is associated with improved outcomes [37]. One potential explanation for a lower ORR with increased FcγRIIa affinity is enhanced binding to sCD30, thereby preventing effective Reed-Sternberg cell binding. FcγRIIIa polymorphisms have also been associated with response and EFS following rituximab [37, 38]. No patients on this trial had a V/V genotype, and in patients with the V/F genotype, no correlation with response was noted. The differences in receptor polymorphisms with respect to SGN-30 and rituximab efficacy may reflect antibody and disease-specific roles of effector cells in antibody-mediated cellular cytoxocity. However, the limited number of samples and the lack of patients with an FcγRIIIa V/V genotype preclude definitive conclusions regarding the correlation of FcγR polymorphisms with response to SGN-30.

In conclusion, the findings from CALGB 50502 indicate that SGN-30 cannot be administered safely with GVD, although further study is needed to determine the mechanism of SGN-30-associated pulmonary toxicity. Humanized anti-CD30 antibodies engineered to enhance Fcγ receptor binding [39, 40] and anti-CD30 antibody drug conjugates [41] are in development. Although the mechanism of Reed-Sternberg cell killing may differ with these agents, combinations with chemotherapy, particularly gemcitabine, should be approached cautiously and further evaluation of the association of FcγR polymorphisms with response and toxicity is warranted. Combinations of anti-CD30 antibodies with salvage chemotherapy regimens that do not contain gemcitabine or the use of anti-CD30 antibodies for minimal residual disease after disease debulking with conventional salvage regimens may prove more tolerable than the combination of SGN-30 with

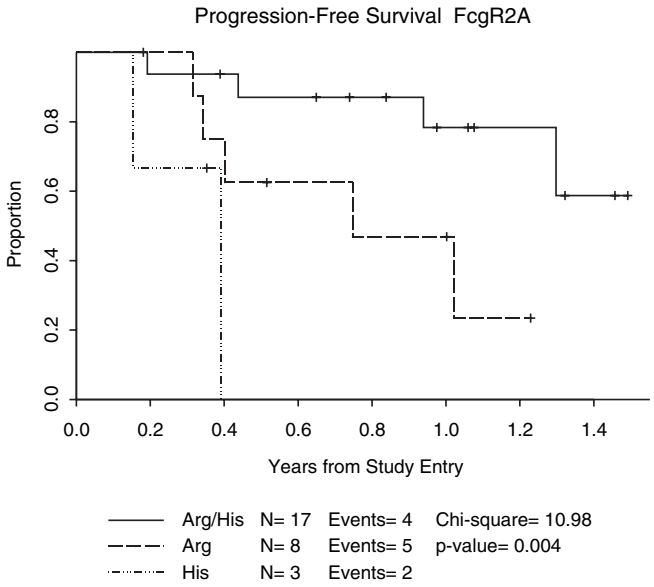

Figure 2. Progression-free survival for patients who are homozygous for histidine (His) expression ($n = 2$, dashed and dotted lines), homozygous for arginine (Arg) expression ($n = 8$, dashed line), and heterozygous (Arg/His, $n = 16$, solid line) after treatment with SGN-30 or placebo and GVD for classical Hodgkin's lymphoma.

GVD. While FcγRIIIa polymorphisms have been implicated in predicting response to monoclonal antibodies, this study represents the first report of the predictive value of these polymorphisms in identifying patients at risk for pulmonary toxicity and these findings should be confirmed in future trials.

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disclosure

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contributions of authors

KAB, BDC, and NLB designed and carried out the study, supervised and enrolled patients on the trial, analyzed and interpreted the data, and authored the manuscript. S-HJ and JLJ developed and carried out the statistical analysis, assisted with manuscript preparation, and reviewed the draft manuscript. EH reviewed the pathological samples and reviewed the draft manuscript. DML and JCB carried out the Fcγ polymorphism analysis, analyzed and interpreted the data, and reviewed the draft manuscript.

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