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CLINICAL TRIAL REPORT

Phase I trial examining addition of gemcitabine to CHOP in intermediate grade NHL

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Abstract
Purpose Gemcitabine induces a 20% response as single-agent therapy in patients with relapsed or refractory NHL. We report phase I findings of gemcitabine in combination with standard CHOP chemotherapy with G-CSF support for intermediate grade NHL. The protocol was modified during enrollment to include rituximab in CD 20+ lymphomas.
Methods Patients received CHOP plus gemcitabine at 500 mg/m^2 (Cohort 1) or 750 mg/m^2 (Cohort 2) on days 1 and 4 of each 21-day cycle. Accrual was suspended once each cohort was filled. Dose escalation occurred after all patients in the cohort were determined to not have a dose-limiting toxicity.
Results Between April 2002 and May 2004, 10 patients were enrolled and completed the study treatment (6 in Cohort 1, 4 in Cohort 2). In Cohort 1, grade 3 toxicities included neutropenia, anemia, neuropathy, and constipation. Grade 4 toxicities were febrile neutropenia and thrombocytopenia. In Cohort 2, grade 3 toxicities included neutropenia, thrombocytopenia, mucositis, anemia, and intestinal obstruction. Grade 4 toxicities included febrile neutropenia, neutropenia, and thrombocytopenia. One patient developed MDS 36 months after chemotherapy. Three of four patients in Cohort 2 developed dose-limiting toxicities (mucositis and thrombocytopenia) requiring dose reduction in gemcitabine after cycle 1. Overall, the survival rate at 2.5 years was 71%.
Conclusions This Phase I trial concludes that gemcitabine 500 mg/m^2 on days 1 and 4 of each 21-day cycle is the maximum tolerated dose when combined with standard CHOP chemotherapy with G-CSF support for intermediate grade NHL.

Keywords Non-Hodgkins lymphoma · Lymphoma · Gemcitabine · NHL

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Introduction

Yearly, an estimated 65,540 new cases of non-Hodgkin's lymphoma (NHL) will be diagnosed, while 20,210 men and women will die of NHL [1]. Multidrug combination chemotherapy regimens have improved the outlook of patients with NHL with the most historically common regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) administered every 3 weeks [2]. Numerous studies sought to find a more curative regimen than CHOP alone. Since rapidity and completeness of response appear to correlate with durability of remission [3], second and third generation combination regimens were established as more intensive alternatives to CHOP chemotherapy in patients with aggressive NHL. However, despite more intensive treatment, no combination regimen was shown to be more beneficial than CHOP [4–10] while some of the second and third generation regimens actually possessed greater toxicities [4, 5].

Recently, new combination regimens have been used with promising results. Trials utilizing ACVBP [11, 12] as well as NHL-15 [13] have shown improved response over CHOP alone in aggressive NHL. These trials did not take into account the addition of rituximab to CHOP, which has been documented to improve response and survival without

substantially increasing toxicity [14–17]. Despite these successes, there are still patients with refractory NHL and the need for novel chemotherapeutic agents. One such novel agent is gemcitabine (2′,2′-difluorodeoxycytidine, dFdC), a pyrimidine antimetabolite with properties similar to cytarabine (ara-C) [18].

Gemcitabine shows cytotoxicity in a variety of human solid tumors including non-small cell lung cancer, breast cancer, pancreatic cancer, bladder cancer, ovarian cancer, and others [19–23]. This distinctive activity profile may be explained by the unique cellular pharmacology of gemcitabine when compared with that of ara-C. Specifically, as a result of its greater membrane permeability and a higher affinity for deoxycytidine kinase, the intracellular concentration and retention of the active metabolite, gemcitabine triphosphate, is significantly greater than that of other pyrimidine analogs [18]. Furthermore, in vitro data indicate that gemcitabine is highly active against NHL and considerably more active against hematologic tumors such as NHL compared with solid tumors [24]. In clinical trials, gemcitabine has been demonstrated to have substantial activity in heavily pretreated patients who have NHL with single-agent response rates of roughly 20–30% [25–30] as well as a response rate of 40–80% in combination therapy [31–38]. Its dose-limiting toxicity is myelosuppression resulting in both thrombocytopenia and neutropenia [18, 28, 33]. Combination modalities have used a gemcitabine dose of 1 g/m^2 with adequate tolerability [31–38]. This trial examines the addition of gemcitabine to standard CHOP and CHOP-R chemotherapy in aggressive NHL.

Materials and methods

Eligibility

Patients between 18 and 75 years of age with histologically proven intermediate grade non-Hodgkin's lymphoma were eligible. Intermediate grade histologies eligible for inclusion were diffuse large cell, follicular predominantly large cell, mantle cell, and anaplastic large cell. Extent of disease was Stage IIB, III, or IV with measurable disease on physical examination or CT. Patients presenting with disease relapse were included in the study design. All patients were ECOG performance status 0 or 1 with no previous treatment with anthracyclines and last radiation treatment greater than 2 weeks prior to study enrollment. For inclusion into the study, an ANC $>$ 1,500/mm^3 and platelet count $>$100,000/mm^3 were required. Patients with known cardiac disease, renal failure (Cr $>$ 2.1), liver failure (total bilirubin $>$ 1.6), and HIV were excluded from the study. Also, excluded were individuals with malignancy in the last 5 years with the exceptions of squamous or basal cell skin cancer and cancer in situ of the cervix. Furthermore, post-transplant lymphoproliferative disorders and patients with serious psychiatric or medical condition that would prevent informed consent were excluded.

Study design/treatment

Patients were assigned in groups of 3 to successive cohorts. All patients received Cyclophosphamide 750 mg/m^2 IV on day 1, Adriamycin 50 mg/m^2 IV on day 1, Vincristine 1.4 mg/m^2 IV on day 1 (maximum dose of 2 mg IV), and Prednisone 100 mg PO on days 1–5. G-CSF 5μg/kg was given on day 5 until ANC $>$ 10,000 in keeping with the relative practice standards at the time. Gemcitabine was given at 500 mg/m^2 (Cohort 1) or 750 mg/m^2 (Cohort 2) on days 1 and 4 of each 21-day cycle. Accrual was suspended once each cohort was filled until dose safety could be reviewed. Dose escalation occurred once all patients in the cohort were determined to not have a dose-limiting toxicity (DLT). DLT was defined as grade 2 mucositis or diarrhea that delayed treatment by 1 week or more, any grade 3 cardiac, renal, hepatic, or neurologic toxicity, and the following hematologic toxicities: febrile neutropenia greater than 48 h, platelet count less than 20,000/μl, absolute neutrophil count less than 500 for 5 or more days, or any delay in the 21-day chemotherapy cycle due to hematologic toxicity. Toxicity was assessed using the NCI CTC version 2.0 (see Table 1).

Patients underwent a minimum of 4 cycles of chemotherapy unless clear progression of disease was seen. Patients who developed CR after 4 cycles were given 2 additional cycles of chemotherapy, and then chemotherapy was discontinued. Patients who developed PR after 4 cycles were given 2 additional cycles of chemotherapy. If these patients went on to develop a CR then they were given an additional 2 cycles for a total of 8 chemotherapy cycles. If these patients remained in PR, they were then taken off of protocol with further treatment given at the discretion of their oncologist. Favorable data on the use of rituximab in aggressive NHL were emerging during the course of enrollment for this trial. However, R-CHOP was not the common practice as the rituximab data had not fully matured. Therefore, the initial protocol using CHOP was amended to include rituximab per the discretion of the treating physician.

Assessment

Response to treatment was assessed by CT scans after completion of the 4th cycle and as indicated. Toxicity assessment with history, physical exam, and CBCs occurred on a routine basis following each chemotherapeutic administration. Furthermore, prior to each cycle patients

Table 1 Dose-limiting toxicities (DLT)

Patient	NHL type	Gemcitabine dose (mg/m^2)	Grade 3 DLT	Grade 4 DLT	Rituximab given	Dose adjustment required
1	Diffuse large cell	500	Thrombocytopenia, neutropenia	None	Yes (adjuvant)	No
2	Mantle cell	500	Anemia, thrombocytopenia, neutropenia	Febrile neutropenia	Yes	No
3	Mantle cell	500	Thrombocytopenia, neutropenia	Febrile neutropenia, thrombocytopenia	No	No
4	Diffuse large cell	500	Anemia, neutropenia	None	Yes (adjuvant)	No
5	Follicular	500	None	None	No	No (only completed 3 cycles)
6	Diffuse large cell	500	None	None	No	No
7	Diffuse large cell	750	Anemia, thrombocytopenia, neutropenia, mucositis	Febrile neutropenia, thrombocytopenia	Yes	Yes (decreased to 500 mg/m^2)
8	Diffuse large cell	750	Thrombocytopenia, neutropenia	None	Yes	No
9	Anaplastic large cell	750	Anemia, thrombocytopenia, neutropenia	Neutropenia, mucositis	No	Yes (decreased to 500 mg/m^2)
10	Diffuse large cell	750	Thrombocytopenia	Thrombocytopenia, neutropenia	Yes (adjuvant)	Yes (decreased to 500 mg/m^2)

underwent physical examination, assessment of performance status, and liver/kidney function tests.

Results

Patients and treatment

Between April 2002 and May 2004, 10 patients were enrolled and completed the study treatment (6 in Cohort 1, 4 in Cohort 2). Six patients had diffused large cell lymphoma (DLCL), 2 had mantle cell lymphoma (MCL), 1 had follicular lymphoma, and 1 had an anaplastic large cell lymphoma (ALCL). Median age was 54.4 years. All but two patients were Stage III or IV. Two patients initially received CVP prior to G-CHOP-G treatment, while 6 patients received rituximab with G-CHOP-G chemotherapy.

Toxicity

In Cohort 1, grade 3 toxicities included neutropenia (3/6 pts), anemia (2), neuropathy (1), and constipation (1). Grade 4 toxicities were febrile neutropenia (2) and thrombocytopenia (1). In Cohort 2, grade 3 toxicities included neutropenia (1/4 pts), thrombocytopenia (2), mucositis (2), anemia (1), and intestinal obstruction (1). Grade 4 toxicities included febrile neutropenia (1), neutropenia (2), and thrombocytopenia (2). One patient developed MDS approximately 36 months after the completion of chemotherapy. Three of four patients in Cohort 2 developed dose-limiting toxicities (mucositis and thrombocytopenia) requiring dose reduction in gemcitabine after cycle 1. One patient in Cohort 2 developed significant thrombocytopenia 10 weeks into the trial to merit discontinuation from the study. The trial was closed based on the dose-limiting toxicities reached in Cohort 2 (see Figs. 1, 2).

Efficacy

Cohort 1 response rates were as follows: 4 CR (1 Mantle Cell, 3 DLCL), 1 Stable Disease (MCL), and 1 unknown

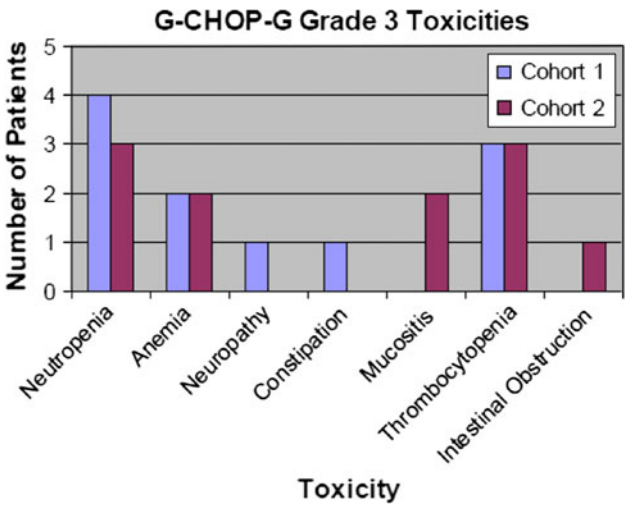

Fig. 1 Grade 3 toxicities encountered during administration of G-CHOP-G

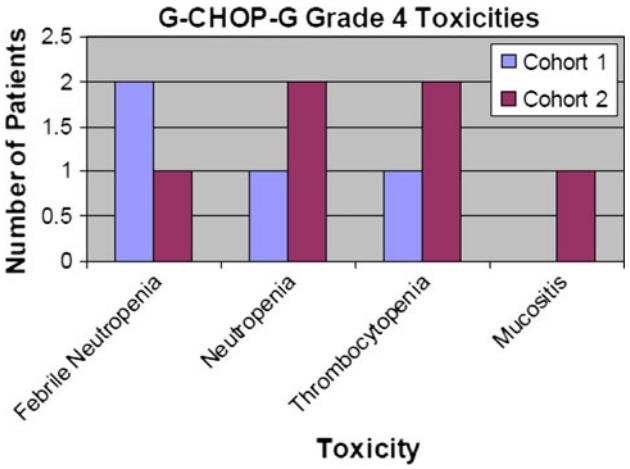

Fig. 2 Grade 4 toxicities encountered during administration of G-CHOP-G

(lost to short-term follow-up). In Cohort 2, there were 3 CR (1 Anaplastic Large Cell, 2 DLCL). The survival rate at 2.5 years was 71% (2 patients from Cohort 1 were excluded as they were lost to long-term follow-up, 1 patient from Cohort 2 was excluded secondary to discontinuation from toxicity).

Discussion

Gemcitabine in combination with other agents have been employed as second-line regimens against NHL with reasonable success [31, 34]. In particular, gemcitabine in combination with vinorelbine has been an effective salvage regimen in aggressive NHL [32]. This Phase I trial concludes that gemcitabine 500 mg/m^2 on days 1 and 4 of each 21-day cycle is the maximum tolerated dose when combined with CHOP chemotherapy and G-CSF support in patients with intermediate grade NHL. Although the study is a relatively small sample size, this gemcitabine dose was well tolerated by all six patients enrolled in Cohort 1, while only 1 of the 4 patients in Cohort 2 tolerated the 750 mg/m^2 dose. Dose-limiting toxicities in the form of thrombocytopenia and neutropenia mirrored previous studies [18, 28, 33]. To date, there has only been one previous study employing gemcitabine with standard CHOP chemotherapy for aggressive NHL [39]. This study concluded that gemcitabine adds significant but tolerable hematological toxicity. However, it also resulted in occasionally severe pulmonary toxicity that in one instance led to death. In contrast, our study had no episodes of pulmonary toxicity. Furthermore, this study concluded that the maximum tolerated dose of 800 mg/m^2 administered on days 1 and 8. Our study utilized a much lower dose of 500 mg/m^2 given over a shorter interval on days 1 and 4.

A critique of our study is that enrollment occurred before rituximab was used in common practice of the treatment of NHL; therefore, the toxicity of gemcitabine when added to CHOP chemotherapy may be underrepresented in our study population. However, of the 10 patients enrolled, 6 received rituximab with 3 of the 6 receiving rituximab concurrently with G-CHOP-G with no increase in toxicity seen in this subset of patients. Future trials could further expand upon the concurrent use of gemcitabine and rituximab in order to determine effects on both toxicity and efficacy. Interestingly, in vitro data support the efficacy of using gemcitabine/rituximab combinations in the treatment of NHL [40, 41].

In this study, response rates are encouraging for this novel chemotherapeutic regimen. The small nature of the study makes conclusions on efficacy difficult, particularly due to the heterogeneity present in the study population. Nevertheless, gemcitabine at 500 mg/2 on days 1 and 4 in combination with standard dose CHOP with G-CSF support is the maximal tolerated dose for this combination in patients with intermediate grade NHL and can be used in future phase II/III studies in order to more fully assess efficacy and late toxicities.

Conflict of interest None.

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