A Study on Relapsed β-Cell Lymphoma in Elderly Patient of Bangladeshi Population with Rituximab, Gemcitabin and Oxaliplatin: an Effective Salvage Regimen

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ABSTRACT

High-dose therapy (HDT) with stem-cell support is the reference treatment for relapsed lymphoma, but is not appropriate for all patients. In Bangladesh High-dose therapy with stem cell support is not yet available. Conventional salvage chemotherapies have been used with limited efficacy and significant toxicity. Rituximab, gemcitabin and oxaliplatin are active as single agents in relapsed or refractory lymphoma, and have demonstrated synergistic effects in vitro and in vivo. Twenty two patients with relapsed or refractory or β-cell lymphoma received up to Six cycle of R-GemOx (rituximab 375mg/m² on day 1, gemcitabine 1000mg/m² and oxaliplatin 100mg/m² on day 2). The majority (60%) had diffuse large β-cell lymphoma. After four cycle of R-GemOx, the overall response rate was 90% (45% complete response (CR)/unconfirmed CR (CRu). High CR/CRu rates were observed in all histological subtypes. In patients who had previously received rituximab, the CR/CRu rate after six cycles was 70%. The 2 year event-free and overall survival rates (median follow-up of 24 months) were 55%, respectively, among responders, the probability of being disease free for 2 years was 70%. Treatment was generally well tolerated. R-GemOx shows promising activity with acceptable toxicity in patients with relapsed/refractory β-cell lymphoma.

Key words: gemcitabine, lymphoma, oxaliplatin, R-GemOx, rituximab

Introduction

Multi agent chemotherapy has been a major advanced in the treatment of non-Hodgkin’s lymphoma. Although some patients can be cured with this approach, disease relapse and refractory disease constitute significant problems for the treatment of all histological subtypes of lymphoma. To date, high-dose therapy (HDT) with hematological stem-cell support is the reference treatment for patients with chemosensitive relapsed aggressive lymphoma. In relapsed indolent lymphoma, this approach also seems superior to conventional salvage chemotherapy. However, many patients cannot benefit from HDT as a result of advanced age, significant co-morbidities previous use of HDT or resistance to salvage chemotherapy. Conventional salvage regiments without HDT, such as dexamethasone, cytarabine and cisplatin (DHAP) or etoposide, methylprednisolone, cytarabine and cisplatin, are associated with poor long-term disease control and significant toxicity. Thus, regiments based on innovative
counts and routine chemistry, including assessment of hepatic and renal function and measurement of lactate dehydrogenase levels.

**Treatment protocol**

Rituximab 375 mg/m² was admitted on day 1 according to the standard infusion rate escalation protocol. Premeditation with methylprednisolone 6 mg/kg i.v., acetaminophen 1000 mg orally and dexchlorpheniramine 6 mg orally was administered to avoid infusion-related side-effects. Gemcitabine 1000 mg/m² (in 500 ml of normal saline) was administered on day 2, at a fixed dose rate of 10 mg/m²/min. This prolonged administered schedule has shown to achieve superior intracellular drug concentrations than the standard 30 min i.v. schedule. Oxaliplatin 100 mg/m² over 2 h was administered on day 2 after gemcitabine. Cycles were repeated every 14 days.

A complete blood count was carried out on days 7, 10 and 14 of each treatment cycle to assess hematological toxicity. Patients underwent clinical examination and routine chemistry assessment before each new cycle. No dose adjustment was planned in the event of hematological toxicity, but cycles were delayed until the absolute neutrophil count reached 1.0 × 10⁹/ℓ and the platelet count reached 100 × 10⁹/ℓ. No dose adjustment of oxaliplatin was required in the event of peripheral neuropathy. In the event of abnormal results by neurological examination or if a patient experienced significant paresthesia lasting for 14 days or more, oxaliplatin was to be stopped until symptoms improved and then restarted at a same dose of 100 mg/m². In the event of pharyngolaryngeal dysesthesia, the duration of the oxaliplatin infusion was to be prolonged from 2 to 6 h. Primary prophylaxis with Granulocyte Colony-Stimulating Factor (G-CSF) was administered with subsequent cycle to aid maintenance of the dose intensity.

**Materials and methods**

**Patient’s selection and evaluation**

Patients were treated at the Oncology Department of Anwer Khan Modern Medical College & Hospital, Dhaka, United Hospital Ltd, Dhaka and City Hospital Ltd, Dhaka. Patients with recurrent or refractory CD20 positive lymphoma of any performance status were eligible for inclusion if there were serious co-morbidities, relapsed & refractory after having conventional R-CHOP or CHOP therapy. Patient was evaluated before treatment by clinical examinations, computed tomography (CT) scans of the thorax, abdomen and pelvis, and bone marrow trephine biopsy. All patients underwent blood sampling for complete blood counts and routine chemistry, including assessment of hepatic and renal function and measurement of lactate dehydrogenase levels.

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Hematological and non-hematological toxicity evaluation was conducted on day 1 of each treatment cycle and included neurological examination and laboratory assessment with
complete blood cell count and serum chemistry tests. Thoracic, abdominal and pelvic CT scans and bone marrow biopsy (in patients with bone marrow involvement at initial diagnosis) were conducted to assess response after both induction therapy and completion of consolidation therapy. After four treatment cycle (induction therapy), patient achieving a complete response (CR), unconfirmed complete response (CRu) or partial response (PR) were eligible for to Two further cycles of R-GemOx (consolidation therapy).

**Statistical methods**

The primary end point of the study was the overall response rate (ORR) after four cycles of treatment. Secondary end points were event-free survival (EFS), defined as the time interval from the date of enrollment in the study until disease progression, relapse or death whichever occurred first and overall survival (OS) calculated from the date of enrollment until death from any cause. For patients who responded after four cycles, time to relapse was defined as the time interval from the date of evaluation until the date of progression or relapse whichever came first. Survival curves were estimated using the product-limit method of Kaplan-Meier and compared using the log-rank test. Relative dose intensity (RDI) for gemcitabine and oxaliplatin was calculated according to Hryniuk et al.18. The Fisher’s exact test was used for comparisons. Statistical tests were considered significant when the two-sided P value was <0.05. Confidence intervals (CIs) were computed with a 95% coverage; CI binominal exact bounds were computed for proportions.

**Results**

From January 2008 to July 2011, 22 patients were enrolled and were eligible for analysis. Median follow-up was 24 months (data cut-off November 30, 2011). Pretreatment patient characteristics are summarized in Figure 1.

![Figure 1: Number of patients in the study](image)

**Treatment exposure**

The overall number of cycles administered was 132 (range, 1-6). Most patients received the intended number of cycles and the median duration of exposure was 12 weeks. No dose reductions were required for rituximab or gemcitabine or oxaliplatin. Seven patients (32%) required a dose delay, most commonly because of peripheral neuropathy and gastrointestinal upset. 3 patients required G-CSF. Of the 110 cycles considered for this analysis (first cycles were excluded), 88 (80%) were delivered on time and at the planned dose. The average RDI was 84% for gemcitabine and 82% for oxaliplatin. Treatment was delayed in a total of 22 cycles; 17 cycles (16%) were delayed because of peripheral neuropathy or neutropenia or thrombocytopenia or gastrointestinal upset and 5 cycles (4%) were delayed because of non-hematological toxicity (febrile neutropenia in four cases and cardiac failure in one case). In total, 20 patients (91%) completed the planned six cycles. Reasons for stopping treatment were severe cardiac failure (one patient) and patient’s request (one after five cycles).

**Response to treatment**

Response rates were calculated after induction therapy (four cycles) and at completion of therapy for patients who completed six cycles. 2 patients progressed during the induction phase. After four cycles, 10 patients achieved a CR, 6 had a CRu and 4 had a PR, resulting in an ORR (CR + CRu + PR) of 90% (95% CI, 75% to 95%). Response rates were similar for the following three histological subtypes: diffuse large B-cell lymphoma (DLBCL), 82% (95%
CI, 65% to 93%); follicular lymphoma (FL), 75% (95% CI, 35% to 97%) and MCL, 100% (95% CI, to 100%). A trend towards a better response rate to induction therapy was observed for rituximab-naive patients compared with those previously treated with rituximab with (95% versus 73%, respectively; P = 0.11). Response rates were lower among patients who had experienced no response to their last treatment or response duration <1 year than among patients who had previous response duration >1 year (53% versus 97%, respectively; P < 0.001). At the end of treatment, 15 patients (70%; 95% CI, 57% to 84%) had achieved a CR/CRu, one patient (4%) had a PR and 6 patients progressed, translating into an ORR of 90%.

Event-free and overall survival
At the time of this analysis (medium duration of follow-up 24 months for the 20 patients who responded to induction treatment), No patients had relapsed, translating into a 2-year progression-free survival of 70% (95% CI, 44% to 85%). For the responders with DLBCL, No relapsed. Of note, for the 19 responders not previously treated with rituximab, the probability of remaining relapse free at 2 years was 81% (95% CI, 61% to 100%) compared with 37% (95% CI, 7% to 68%; P < 0.05) for the 19 patients previously treated with rituximab. Kaplan-Meier curves for OS and EFS are shown in Figure 1. With a median follow-up of months, the 2 years EFS and OS rates were 43% (95% CI, 27% to 60%) and 66% (95% CI, 50% to 82%), respectively. The median time to progression (TtP) was 22 months (range, 1-24 months). No patient died during the treatment period. Among patients with DLBCL, the 2 years EFS was 42% (95% CI, 22% to 62%) and the median TtP was 24 months, with no significant difference between patients previously treated with rituximab and rituximab-naive patients (median TtP of 16 and 24 months, respectively).

Safety
No fatal toxicity was observed. Treatment was generally well tolerated, with the majority of patients hospitalized for only one night with the first administration of rituximab during the first cycle of treatment. Neutropenia grades 2, 3 and 4 were reported in 33%, 22% and 11% of cycles, respectively, while thrombocytopenia grades 2, 3 and 4 were reported in 12%, 19% and 4% of cycles, respectively. Febrile neutropenia was observed in 4% of cycles. Grade 2 neutrotoxicity occured in 45% of cycles, but no grade ¾ neutrotoxicity was reported. Two patients (4%) received red cell transfusions with a median of 1 (range, 2-6) .No renal toxicity was observed. No other grade ¾ non-hematological toxicity was observed.
**Discussion**

In this study of 22 patients with relapsed or refractory β-cell lymphoma, four cycles of R-GemOx achieved a high ORR of 90%. These results compare favorably with data for conventional chemotherapy regimens, which show low response rates and few durable responses[^3]. Our results also similar with those of other combinations of rituximab and chemotherapy in the relapsed/refractory setting: Kewalramani et al.[^10] reported a 90% ORR and 70% CR rate in a population of 20 younger patients treated with rituximab, ifosamide, carboplatin and etoposide, none of whom had been previously exposed to rituximab. Jermann et al.[^11] reported a 68% ORR and 28% CR rate with the rituximab, etoposide, doxorubicin, vincristine, cyclophosphamide and prednisolone regimen in a population of 50 patients among which 4% had receive prior rituximab. At the end of treatment, very high ORR and CR/CRu rates were seen in patients who had not previously received HDT (90% and 70%, respectively). The R-GemOx regimen had a very favorable toxicity profile. No nephrotoxicity was seen, and hematological toxicity was manageable with the help of growth factor support. Rates of compliance and delivery of the intended number of cycle at the intended dose were good. There were few infections and no deaths. Oxaliplatin-associated neurotoxicity occurred in only 45% of cycles and no grade ¾ neurotoxicity was observed. These results are particularly encouraging for the treatment of elderly patients with lymphoma. Each component of the R-GemOx regimen may contribute to its efficacy; indeed, the results of this study support a synergistic or supra-additive action for rituximab when combined with gemcitabine and oxaliplatin. This observation is consistent with results from previous student in lymphoma and other cancers. The use of R-GemOx is currently under further investigation in a larger, multicenter study being conducted by the group d’Études Lymphomes de l’Adulte in patients with relapsed/refractory β-cell lymphoma, with DLBCL. In conclusion, the R-GemOx regimen shows promising activity with an acceptable toxicity profile, and may be a favorable treatment option for patients of Bangladesh with relapsed/refractory β-cell lymphoma as High-dose therapy with stem cell support is not yet available.

**References**


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**Conclusion**

In this study of 22 patients with relapsed or refractory B-cell lymphoma, four cycles of R-GemOx achieved a high ORR of 90%. In Bangladesh we know that stem cell support with HDT is not available. So, for elderly with comorbid, relapsed cases of β-cell lymphoma is difficult to manage. This study is encouraging for such population of patient in Bangladesh. This result also support favorable data for conventional chemotherapy regimen for which show low response rate and few durable responses[^3]. The R-GemOx regimens have a very favorable toxicity profile. Haematotoxicity was well managed with G-CSF. Neurotoxicity was negligible. There was no serious infection. No treatment related death was found. R-gemox therapy for elderly relapsed and refractory β-cell lymphoma is encouraging with good response and acceptable toxicity profile. Further study may be encouraged to treat β-cell lymphoma patient with R-GemOx therapy in other settings including initial treatment also.


