Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt’s lymphoma: a retrospective analysis

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Background: Burkitt’s lymphoma (BL) is a highly aggressive B-cell non-Hodgkin’s lymphoma (NHL) that may be cured with intensive chemotherapy. The addition of the CD20-directed monoclonal antibody rituximab to CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate, alternating with ifosfamide, etoposide, and cytarabine) has not been studied despite efficacy in other aggressive CD20-positive NHLs.

Patients and methods: Eighty adult BL patients treated with or without rituximab were identified at our institutions. Response rate, overall survival (OS), and progression-free survival (PFS) are calculated.

Results: There were fewer relapses in rituximab-treated patients (3 of 40 versus 13 of 40, $P = 0.01$). There was a trend for improvement in outcome favoring rituximab-containing therapy, with 3-year PFS (74% versus 61%) and 3-year OS (77% versus 66%), although these did not reach statistical significance. Advanced age and central nervous system involvement were associated with poorer OS on multivariable Cox regression analysis, adjusting for treatment, human immunodeficiency virus (HIV) involvement, and risk group.

Conclusions: CODOX-M/IVAC, with or without rituximab, is a highly effective regimen for the treatment of adult BL. Rituximab decreased the recurrence rate and showed a trend in favor of improvement in PFS and OS. HIV-infected patients achieved outcomes comparable with those of their non-HIV-infected counterparts.

Key words: AIDS, Burkitt’s lymphoma, HIV, Magrath regimen, non-Hodgkin’s lymphoma, rituximab

introduction

Burkitt’s lymphoma (BL) is a highly aggressive B-cell non-Hodgkin’s lymphoma (NHL) accounting for nearly 3% of all newly diagnosed NHLs [1]. Several intensive treatment programs are presently employed worldwide for BL in adults, all of which incorporate both systemic and central nervous system (CNS)-directed therapy. One of the most common treatment regimens is the short-course intensive CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate, alternating with ifosfamide, etoposide, and cytarabine), which has undergone several modifications to improve the toxicity profile and preserve efficacy in adults [2–5]. Adult BL patients treated with this regimen have complete response rates (CRRs) of 75%–85%, with ~65% of patients cured of their disease. Patients with low-risk disease, defined as having a single site of disease <10 cm and normal lactate dehydrogenase (LDH) level, or completely resected disease, are treated with three cycles of CODOX-M and have an improved prognosis compared with high-risk patients who receive four alternating cycles of CODOX-M and IVAC. No prospective trial of CODOX-M/IVAC has included patients with human immunodeficiency virus (HIV) positivity, a dominant risk factor for development of BL in adults, although small series suggest that these patients can achieve similar outcomes as their HIV-negative counterparts [6–8].

The CD20-directed monoclonal antibody rituximab has been shown to improve overall survival (OS) when added to standard chemotherapy for low-grade B-cell lymphomas and diffuse large B-cell lymphoma (DLBCL) [9–11]. In contrast to these diseases, data regarding the role of rituximab in BL are limited [12, 13]. Rituximab has been combined safely in a small series of BL patients treated with hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, and cytarabine) [14–16], but no data have yet been published with CODOX-M/IVAC. We present the first experience of the combination of rituximab with CODOX-M/IVAC in adult BL patients, with or without HIV infection, compared with historical controls treated before the inclusion of rituximab.
methods

study design

We queried our institutional review board-approved comprehensive clinicopathological database of hematologic malignancy patients at the Massachusetts General Hospital and the Dana-Farber Cancer Institute for all adult BL patients diagnosed and treated at our institutions from 1 December 1992 through 1 December 2009. One hundred four cases of BL were identified. Subjects were then selected for inclusion in our analysis if they received modified CODOX-M/IVAC chemotherapy [4], with or without rituximab. Eighty subjects met the inclusion criteria and are included in the analysis. Details of the diagnosis including cytogenetics, immunophenotype, and proliferation index were obtained from the medical record where available. The pathological diagnosis of BL was based on review by expert hematopathologists using the current Revised European-American Lymphoma (classification system) or World Health Organisation criteria at the time of diagnosis.

treatment

Subjects treated with rituximab-containing therapy received one infusion per cycle at 375 mg/m², in addition to the modified CODOX-M/IVAC regimen, which has been shown to be similarly effective as the original regimen published by Magrath et al. [4]. Modifications to the original CODOX-M/IVAC regimen included the following: adjustment of cyclophosphamide schedule to 800 mg/m² on days 1 and 2, vincristine capped at 2 mg total, increase in doxorubicin dose from 40 to 50 mg/m², decrease in i.v. methotrexate dose from 6.7 to 3 g/m², and decrease in intrathecal cytarabine dose from 70 to 50 mg. Patients with low-risk disease (defined as a single focus of disease <10 cm with a normal LDH level) received three cycles of CODOX-M with or without rituximab. Patients with high-risk disease received alternating CODOX-M and IVAC with or without rituximab for four cycles. All patients received intrathecal methotrexate and cytarabine in addition to systemic methotrexate and cytarabine for CNS prophylaxis. Patients with CNS involvement at presentation (defined as positive cytology, flow cytometry, or characteristic magnetic resonance imaging findings) were treated with additional intrathecal chemotherapy, as per the published protocol [4]. All subjects received routine growth factor support with granulocyte colony-stimulating factor and *Pneumocystis jiroveci* prophylaxis.

statistical analysis

Primary end points were OS and progression-free survival (PFS). OS was defined as time from initial diagnosis to death from any cause. PFS was defined as time from initial diagnosis to progression or death. Kaplan-Meier estimates of PFS and OS were calculated along with their corresponding 95% confidence intervals (CIs). Multivariable Cox regression models of OS and PFS were used to provide adjusted treatment comparisons and identify simultaneous significant prognostic factors. Responses were assessed based on the original radiology reports. The overall response rate (ORR) was defined as the number of subjects with either complete response (CR) or partial response (PR). Comparison of patient characteristics and ORR between treatment groups was analyzed using Fisher’s exact test with a two-sided significance level of 0.05.

results

patient characteristics

Forty patients received rituximab in addition to chemotherapy (R-CODOX-M/R-IVAC), compared with 40 patients treated with CODOX-M/IVAC alone. The median age was 46 years (range 17–78 years), and most patients were male (79%). The majority of patients had advanced Ann Arbor stage (73%), elevated LDH level (71%), and extranodal involvement (80%). Thirteen patients (16%) were classified as low risk, and the remaining 67 (84%) had high-risk disease. Fourteen patients (18%) were HIV positive, 13 of whom received concurrent highly active antiretroviral therapy (HAART). The median CD4 count in HIV-positive patients was 237 (50–469), with a median viral load of 22 604 (range 0–329 000). Fifteen patients (19%) had CNS involvement at the time of diagnosis. Cytogenetics was available in 39 (98%) of rituximab-treated patients, with 38 (95%) harboring an 8;14 translocation. Cytogenetics was available in only 24 (60%) of chemotherapy-alone patients, with 19 (48%) harboring an 8;14 translocation. In the rituximab-treated patients, six had both 8;14 and 14;18 translocations compared with none in the chemotherapy-alone group likely reflecting the evolution of diagnostic testing during the study period. Patient characteristics are summarized in Table 1. There were no significant differences between the groups.

outcomes

The ORR for all patients was 89%, with a CRR of 88% (Table 2). Seven patients (9%), three in the rituximab-treated group and

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tr>
<td>All patients, N = 80 (%)</td>
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<tr>
<td>Sex (M:F)</td>
</tr>
<tr>
<td>Median age (minimum–maximum), years</td>
</tr>
<tr>
<td>Serum LDH &gt;upper limit of normal</td>
</tr>
<tr>
<td>Ann Arbor stages III–IV</td>
</tr>
<tr>
<td>No. of extranodal sites &gt;1</td>
</tr>
<tr>
<td>Any extranodal involvement</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>Bulky tumor (&gt;10 cm)</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
</tr>
<tr>
<td>CNS involvement</td>
</tr>
<tr>
<td>HIV positive</td>
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<tr>
<td>Median CD4 count (range)</td>
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<td>Median viral load (range)</td>
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M, male; F, female; LDH, lactate dehydrogenase; CNS, central nervous system; HIV, human immunodeficiency virus.
four treated without rituximab, had primary refractory disease and did not achieve remission. Four patients (5%), three in the rituximab-treated group and one treated without rituximab, died due to infection during treatment. At a median follow-up of 40.3 months (range 3.5–131.3 months), the 3-year PFS and OS for the entire cohort are 68% (95% CI 57% to 68%) and 71% (95% CI 61% to 81%), respectively (Figure 1).

**impact of rituximab**

Forty patients received R-CODOX-M/R-IVAC, compared with 40 patients treated with CODOX-M/IVAC alone. The median number of total rituximab doses was four, with a range of one to six. Rituximab was most commonly administered on day 1 of each cycle, with the exception of cycle 1 when it was administered on day 3 to minimize risk of tumor lysis syndrome. Twenty-nine patients (72%) received four total doses of rituximab, seven (18%) patients received three doses, and one patient each received one, two, five, or six doses. The majority of patients completed all planned therapy, 88% with rituximab and 85% without rituximab. The ORR was 90% in patients treated with rituximab and 88% in those treated without rituximab. Thirty-six patients (90%) achieved CR in the rituximab group compared with 34 (85%) patients treated without rituximab ($P = 0.37$). The median follow-up in R-CODOX-M/R-IVAC patients was 31.5 months (range 3.7–54.6 months), compared with a median follow-up of 60.6 months (range 3.5–131.3 months) in patients treated with CODOX-M/IVAC alone. The 3-year PFS was 74% for R-CODOX-M/R-IVAC, compared with 61% for CODOX-M/IVAC alone ($P = 0.30$). The 3-year OS was 77% in rituximab-treated patients compared with 66% in patients treated with chemotherapy alone ($P = 0.43$) (Figure 2).

**multivariable analysis**

Results for the multivariable Cox regression models for OS and PFS are summarized in Table 3. CNS involvement was associated with a threefold increased risk for death (95% CI 1.18–7.80, $P = 0.02$) but no difference was seen in terms of PFS. Age $>60$ years was associated with both a threefold increased risk for progression (95% CI 1.2–7.71, $P = 0.02$) and a 3.84-fold increased risk for death (95% CI 1.47–10.0, $P = 0.01$). Treatment with rituximab, risk group, and HIV infection were not statistically significant.

**relapses**

There were a total of 16 relapses (20%). Fewer relapses were observed among rituximab-treated patients compared with patients treated with chemotherapy alone (3 versus 13, $P = 0.01$). Four patients of the 16 who relapsed successfully achieved a second remission. Two patients were treated with high-dose chemotherapy and autologous stem cell support. One patient treated with chemotherapy alone had an unusually late relapse at 5 years, raising the likelihood of a second primary lymphoma. A second relapsed patient treated with chemotherapy alone initially tolerated only one cycle of CODOX-M due to infectious complications but was able to achieve a CR; he relapsed 7 months later and was treated with dose-reduced CODOX-M/IVAC.
Of the 13 patients with low-risk disease, 6 patients experienced grade 4 neutropenia, with 4 patients requiring admission for neutropenic fever. Two patients developed grade 4 thrombocytopenia. There were no treatment-related deaths in the low-risk group. Among 67 patients with high-risk disease treated with alternating cycles of CODOX-M/IVAC, with or without rituximab, 66 (99%) developed grade 4 neutropenia, with 47 high-risk patients (70%) experiencing at least one episode of neutropenic fever. Sixty-six (99%) patients experienced grade 4 thrombocytopenia. There were seven cases of tumor lysis syndrome resulting in renal failure, five in patients treated without rituximab and two in patients treated with rituximab. There were eight cases of sepsis, three cases in HIV-negative patients treated without rituximab, two in HIV-positive patients treated with rituximab, and three in HIV-negative patients treated with rituximab.

Given concern that inclusion of rituximab may impair marrow recovery and delay treatment cycles, we assessed the mean cycle lengths with the addition of rituximab versus not, and found no difference for either low-risk (19 versus 21 days) or high-risk (23 versus 22 days) patients. There was also no difference in the number of patients able to complete all planned therapy (37 versus 34).

There were 24 deaths in this series, 9 in the R-CODOX-M/R-IVAC group and 15 in the CODOX-M/IVAC group. Six deaths were treatment related, four of which were in rituximab-treated patients. Of the nine deaths in the rituximab group, three were due to primary refractory disease, two due to relapse, three due to infectious complications related to treatment, and one due to therapy-related myelodysplastic syndrome occurring 18 months after completion of therapy. Of the three infectious-related deaths in the rituximab group, one patient was HIV positive and two were not. Of the 15 deaths in the chemotherapy-alone group, 10 were due to progressive disease after relapse, 4 due to primary refractory disease, and 1 due to infectious complications.

discussion

We present a retrospective analysis of the addition of rituximab to CODOX-M/IVAC in adult patients with BL. We identified 80 patients at our institutions treated with CODOX-M/IVAC alone. The CRR is 88% and 3-year PFS and OS are 68% and 71%, respectively. The CRR for rituximab-treated patients in this series was 90%, with 3-year PFS and OS of 74% and 77%, which compares favorably to prior reports of CODOX-M/IVAC alone [2–4]. Comparing the rituximab-treated patients with those who received CODOX-M/IVAC alone, no statistically significant differences were observed in our series, although there was a trend in favor of superiority of rituximab-containing therapy in all efficacy end points, including 3-year PFS (74% versus 61%) and 3-year OS (77% versus 66%). In addition, fewer relapses were observed among rituximab-treated patients compared with...
chemotherapy alone (3 versus 13, \( P = 0.01 \)). Prior reports of CODOX-M/IVAC without rituximab demonstrate slightly inferior outcomes, with PFS consistently \(~66\%\) across multiple series. Our results appear favorable despite our inclusion of increased numbers of older, high-risk, HIV-positive patients and those with CNS involvement than in prior series. The trend toward improvement in outcome in our rituximab cohort compared with non-rituximab-treated patients, and particularly the lower recurrence rate, suggests that a larger series may yet reveal a statistically significant benefit. Other high-intensity regimens have suggested improvement in BL when combined with rituximab [6, 14]. The combination of eight doses of rituximab with the hyper-CVAD regimen yielded results similar to our series [14]. When patients treated with R-hyper-CVAD were compared with historical patients treated with hyper-CVAD alone, there was a significant reduction in relapse rate, favoring the inclusion of rituximab (7\% versus 34\%, \( P = 0.008 \)), and an improved 3-year OS (89\% versus 53\%, \( P \leq 0.01 \)) [14]. Eight doses of rituximab have also been combined with an intensive chemotherapy regimen in a cohort of HIV-positive and HIV-negative patients with similar results, including a CRR of 88\% and 84\%, respectively [6]. Two-year OS was 82\% in HIV-positive patients and 77\% in HIV-negative patients [6]. Five of 36 patients in that trial died during treatment, 4 due to infectious complications [6]. Patients in our series received a maximum of six doses of rituximab, with a majority receiving four doses, one with each chemotherapy cycle. Whether more doses of rituximab included with short-course high-intensity chemotherapy like CODOX-M/IVAC would confer additional benefit is unknown.

There was a trend toward more infectious-related deaths in the rituximab group, but the overall rate of infections was not different between the two groups, and the low sample size is not sufficient to determine whether rituximab truly increased the rate of infection-related mortality. Less intensive therapy with CHOP-like (combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone) regimens would offer less toxicity but also significantly decrease the chance of cure for BL compared with intensive therapy [17]. Infusional therapy with dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) has been reported to be highly effective with a lower risk profile in adult BL, although patients in that series were predominantly young with low-risk features including normal LDH level and absence of CNS involvement [15]. At present, high-intensity therapy, with the attendant increased risks for morbidity and mortality, remains the standard first-line therapy for adult BL, but the role of lower intensity regimens remains an important question for prospective evaluation, particularly in older and low-risk BL patients.

Few series have reported the outcome of HIV-associated BL patients treated with intensive chemotherapy. Our study includes 14 HIV-positive patients and finds no significant impact of HIV status on PFS and OS. CD4 counts were above 200 in the majority of patients, as is typical of HIV-associated BL, and 13 of 14 HIV-infected patients were treated with concomitant HAART. Among 14 patients with HIV-associated BL in our series, the 3-year PFS and OS were 68\% and 68\%, respectively. One prior retrospective study evaluated CODOX-M/IVAC without rituximab in eight HIV-positive BL patients and found an event-free survival of 60\%, which was not significantly different from that of their matched cohort of HIV-negative BL patients [7]. Other series have investigated hyper-CVAD as well as an intensive rituximab-containing chemoinmunotherapy regimen, with no difference in toxicity or efficacy in HIV-infected individuals [6, 8]. Our study, in concert with these previous reports, demonstrates that HIV-positive patients with BL can be treated with intensive rituximab-containing regimens and concurrent HAART therapy with similar outcomes as HIV-negative patients.

This study is limited by its retrospective nature, but there are no prospective studies published to date examining the role of rituximab in concert with CODOX-M/IVAC. Patient selection in this series was based on diagnosis by hemopathology experts at the time of diagnosis. The definition of BL and diagnostic testing have evolved over the time period of our study, which may result in inclusion of patients who would not be defined as having BL today but rather with high-grade B-cell lymphoma with intermediate features between DLBCL and BL [18]. This is reflected by the increased number of patients with cytogenetics and Ki67 staining available in the more recently treated rituximab cohort. Gene expression profiling studies have shown that pathological diagnosis of BL is imperfect, even by expert hematopathologists, and that molecular classifiers may not agree with a hematopathological diagnosis [17, 19]. In the absence of molecular classification in the clinic, however, BL remains a clinicopathological diagnosis. The relatively recent role of rituximab in this disease results in shorter follow-up of the rituximab-treated patients compared with the chemotherapy-alone patients (31 versus 60 months), although relapses after 18 months in BL are extremely rare, so this likely has no impact on our results.

Our results confirm that CODOX-M/IVAC, with or without rituximab, is a highly effective regimen for the treatment of adult BL, although at the cost of hematologic and infectious toxicity. Presence of advanced-age disease and CNS involvement are associated with an inferior prognosis, consistent with findings from prior studies, although notably even the highest risk patients may be cured of their disease. HIV infection is not an adverse risk factor, and infected patients should be treated with aggressive therapy akin to their HIV-negative counterparts. Rituximab appears to add benefit to CODOX-M/IVAC, although the optimal dose and schedule remain undefined and will ideally be studied in prospective treatment trials.

disclosure

EHP reports consulting and speaking fees from Genentech. There are no other conflicts of interest.

references


