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Addition of Rituximab to High-Dose Methotrexate-Based Chemotherapy Improves Survival of Adults with Burkitt Lymphoma/Leukemia

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Burkitt lymphoma/leukemia (BL) is a very aggressive B-cell lymphoid neoplasm. Results of BL treatment have been substantially improved by the introduction of high-dose methotrexate-based chemotherapy, with survival rates in adult patients with disseminated disease ranging from 40 to 60% [1]. Although tumor cells express CD20, there is a dearth of data on the effect of rituximab in BL. Here we present our experience with the treatment of adult BL patients using a high-dose methotrexate- and rituximab-containing regimen.

This is a retrospective study performed by chart review. Between 2000 and 2011, 20 immunocompetent adult patients with newly diagnosed sporadic BL, stage II–IV, (table 1) were treated in our center using a modification of the B-NHL 86 regimen developed by the German Multicenter Study Group for the Treatment of Adult ALL (GMALL) [2]. From 2006 all patients also received rituximab. Eight patients were treated without and 12 with rituximab. BL was diagnosed according to the REAL or WHO criteria [3–5]. Patients with Burkitt-like lymphoma according to the REAL classification or grey-zone lymphoma according to the newer WHO criteria were not included in this analysis. Prior to treatment all patients underwent routine staging, including CT scanning and bone marrow biopsy. The response was evaluated after 2 cycles and after the end of chemotherapy using CT-based criteria. Treatment consisted of a prephase containing steroids and cyclophosphamide followed by 6 alternating A and B cycles containing high-dose methotrexate, ifosfamide, vincristine, cytarabine, cyclophosphamide, doxorubicin and etoposide and intrathecal CNS prophylaxis (table 2). Rituximab was administered once per cycle at the standard dose of 375 mg/m^2. Areas not in CR after chemotherapy were irradiated with 30–36 Gy. (Immuno)chemotherapy was administered in hospital. Patients were then discharged and readmitted if serious complications occurred or for the next treatment cycle. All received standard supportive care including G-CSF, blood product transfusions, antibiotics, and acyclovir.

Statistical evaluation was performed using SPSS, version 14 (LEADTOOLS©; LEAD technologies, USA). Sur-

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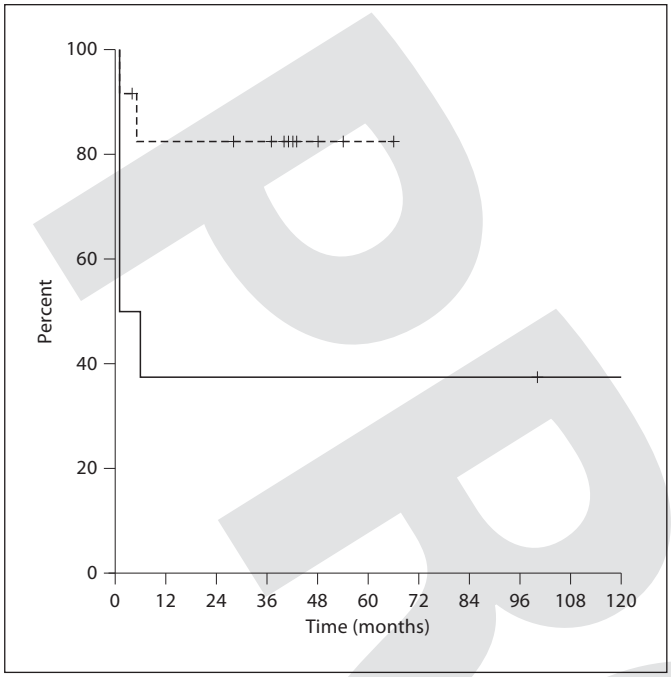

Fig. 1. OS (%) of patients treated with (dotted line) and without rituximab (full line).

Table 1. Patients' characteristics

	Chemotherapy only	Rituximab + chemotherapy	Total
Gender (M/F)	6/2	10/2	16/4
Median age (range), years	32 (16–63)	36 (16–59)	35 (16–63)
Stage (II/III/IV)	0/1/7	2/2/8	2/3/15
IPI (0–2/3–5)	1/7	4/8	5/15
CNS involvement	0	1	1

Table 2. Chemotherapy regimen

Prephase
- Cyclophosphamide: 200 mg/m^2 on days 1–5
- Prednisone: 60 mg/m^2 on days 1–5

Block A
- Vincristine: 2 mg on day 1
- Methotrexate: 1.5 g/m^2 on day 1 with folinic acid rescue
- Ifosfamide: 800 mg/m^2 on days 1–5 with uromitexan
- Etoposide: 100 mg/m^2 on days 4, 5
- Cytarabine: 150 mg/m^2 every 12 h on days 4, 5
- Dexamethasone: 10 mg/m^2 on days 1–5

Block B
- Vincristine: 2 mg on day 1
- Methotrexate: 1.5 g/m^2 on day 1 with folinic acid rescue
- Cyclophosphamide: 200 mg/m^2 on days 1–5
- Doxorubicin: 25 mg/m^2 on days 4, 5
- Dexamethasone: 10 mg/m^2 on days 1–5

CNS prophylaxis
- Methotrexate: 15 mg intrathecally once per cycle
- Cytarabine: 40 mg intrathecally once per cycle
- Methylprednisolone: 40 mg intrathecally once per cycle

vival functions were calculated using the Kaplan-Meier method. The assumed level of significance was 0.05. The analysis was approved by the Ethics Committee of the Medical School of the University of Zagreb, Croatia.

The toxicity of the treatment was substantial. Three patients, one in the rituximab group and two in the chemotherapy-only group, died early after diagnosis due to tumor lysis syndrome and multiple organ failure. All other patients except one had to be readmitted between cycles because of febrile neutropenia or severe mucositis. One patient treated with rituximab and one treated without rituximab died of infection. There were no cases of secondary cancer or serious late treatment-related toxicity.

After the initial response, two patients in the chemotherapy-only group relapsed while on treatment and died shortly thereafter. The remaining three patients achieved remission. Ten patients treated with rituximab achieved remission. The difference in response between the two groups is statistically significant (38 vs. 83%, p = 0.035, χ^2 test).

None of the responding patients relapsed after the end of treatment. With a median follow-up of 39 months for all patients and 43 months for survivors, the overall (OS) and progression-free survival (PFS) was 64%. The OS and PFS in the chemotherapy-only group was 38% and in the rituximab treated group it was 83% (p = 0.039, log-rank test) (fig. 1).

This was a retrospective study with a historical control and a very limited number of patients, and thus a number of possible biases potentially favoring the rituximab-treated group were introduced. However, there were no apparent differences between the two groups regarding possible prognostic factors such as age, stage, LDH, bulky disease, or IPI([redacted]), and the difference in outcome seems to be caused by increased treatment efficacy since there were no cases of refractory disease in the group treated with rituximab. The number of reports on the outcome of immunocompetent adult BL patients treated with rituximab and high-dose methotrexate-based chemotherapy is, to our knowledge, limited [6–11]. Despite

differences in chemotherapy, the results of all of these studies are very similar to ours, with OS and PFS rates between 74 and 89%. None of the trials was randomized, but the toxicity of rituximab is negligible and the prognosis of BL patients failing front-line treatment is dismal. Moreover, one patient with localized disease seemed to be cured with rituximab monotherapy [12]. We therefore believe that all adult patients should receive rituximab combined with chemotherapy. High-dose methotrexate-based regimens remain considerably toxic and meticulous supportive care is needed to keep the toxicity-related morbidity and mortality within acceptable limits.

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