Malignant Lymphomas

The effect of pre-irradiation dose intense CHOP on anthracyline resistance in localized nasal NK/T-cell lymphoma

We treated 17 patients with localized, nasal NK/T-cell lymphoma with two cycles of dose-intense CHOP (DI-CHOP) and early involved field radiation (IFRT). Sixteen out of 17 patients were evaluable for response. After two cycles of DI-CHOP, nine patients achieved complete remission (CR) (53%) and six had partial remissions (35%). After IFRT, 13 patients achieved CR (CR rate 76%; 95% CI, 56%-96%). The 3-year progression-free and overall survival rates were 56%, and 67%, respectively. This study shows that anthracycline-based chemotherapy seems to be ineffective in decreasing systemic failure even when administered at maximal dose intensity.

haematologica 2006; 91:427-428
(*http://www.haematologica.org/journal/2006/03/427.html*)

Most patients with nasal NK/T-cell lymphoma (NTCL) present with stage I/II with an International Prognostic Index score of 1 or less. However, only 30-60% of the patients survive disease-free.[1-6] Complete response and overall survival rates seem to be better after up-front radiation therapy than after chemotherapy.[2,6] However, it was previously reported that radiation alone was suboptimal because of a high rate of systemic failure.[3] Based on our experience, four cycles of standard CHOP followed by involved field radiation (IFRT) was not satisfactory.[5] In order to improve treatment outcome, we escalated the dose intensity of CHOP chemotherapy[7,8] and administered radiation therapy early in treatment.

From March 2000 to June 2004, 17 newly diagnosed patients with stage I or II non-bulky nasal NTCL were enrolled. All patients were older than 18 years, had an ECOG performance status (PS) of 0 to 2, and had measurable lesions. The treatment consisted of two cycles of dose-intense CHOP (DI-CHOP) followed by early IFRT (44 Gy, within 4-6 weeks after the DI-CHOP) and four cycles of standard CHOP as consolidation therapy. The DI-CHOP regimen consisted of 1250 mg/m^2 of cyclophosphamide, 75 mg/m^2 of doxorubicin, 1.4 mg/m^2 of vincristine (2 mg as a capping dose) on day 1 and 100 mg/day of prednisolone for 5 days. DI-CHOP chemotherapy was repeated every 2 weeks. Prophylactic granulocyte colony-stimulating factor was administered from day 3 to day 12. DI-CHOP was started when the absolute neutrophil exceeded 1500/mm^3 and the platelet count was greater than 75,000/mm^3, and non-hematologic toxicity had recovered to grade 0 or 1. The total dose of 44 Gy radiotherapy was administered using a conventional fractioned schedule (2.0 Gy/fraction, 5 fractions/week) to prechemotherapy gross disease.[5]

The clinical characteristics of the 17 patients are given in Table 1. Six patients had advanced primary lesions (bone destruction in four and skin infiltration in two). All except one received two cycles of DI-CHOP. The median day of the second cycle of DI-CHOP was 15 days (range, 13-23). There was one treatment-related death after the first cycle of DI-CHOP. All patients who received two cycles of DI-CHOP received IFRT. Post-radiation CHOP was not administered in five patients (three had disease progression and two refused). During DI-CHOP, no dose reduction was required, but treatment was delayed in five patients. The average dose intensity of DI-CHOP was 35.8 mg/m^2/week (95% of planned dose intensity) for doxorubicin and 595.9 mg/m^2/week (95% of planned dose intensity) for cyclophosphamide. Sixteen patients were evaluable for response. After two cycles of DI-CHOP, there were 9 complete remissions (53%) and six partial remissions (35%). Three patients in partial remission after DI-CHOP progressed after IFRT. Eventually, 13 patients achieved complete remission after the completion of treatment (complete remission rate 76%; 95% CI, 56%-96%). The 3-year progression-free survival and overall survival were 56%, and 67%, respectively (Figure 1). Grade 4 neutropenia was observed in ten patients (59%) during DI-CHOP. One patient died of neutropenic sepsis, and another seven patients (41%) experienced febrile neutropenia. Non-hematologic toxicity was mild to moderate in most patients. One patient developed grade 3 stomatitis during DI-CHOP. In relation to IFRT, no patient experienced grade 3 stomatitis, but one patient developed grade 3 emesis. During the follow-up period, treatment failed in eight patients including one who died of treatment-related causes. Three patients progressed after completion of IFRT. Two patients had systemic failure and one patient had locoregional failure. Another four patients relapsed after completion of the planned treatment. Three of these patients had systemic failure and one had locoregional failure.

Short course DI-CHOP was feasible in these patients. Most of the patients were able to receive the second cycle of DI-CHOP without significant delay. However, com-

Table 1. Patients' characteristics.

Characteristics	*Number of patients (%)*
Eligible/total patients	17/17
Age (years)	
Median	53
Range	37-65
Sex	
Female	4 (24)
Male	13 (76)
Age	
≤ 60 years	13 (76)
> 60 years	4 (24)
Performance status (ECOG)	
0-1	16 (94)
2	1 (6)
Stage	
IA/IB	10 (58) / 4 (24)
IIA/IIB	3 (18) / 0 (0)
LDH > normal	4 (24)
Primary site	
Nasal cavity	11 (64)
Nasopharynx	2 (12)
Nasal cavity & nasopharynx	4 (24)
Primary lesion extent	
Bony destruction	4 (24)
Skin infiltration	2 (12)
International prognostic index	
Low risk	14 (82)
Low-intermediate risk	2 (12)
High-intermediate risk	1 (6)
EBV *in situ* hydridization (+) (n=14)	14 (100)

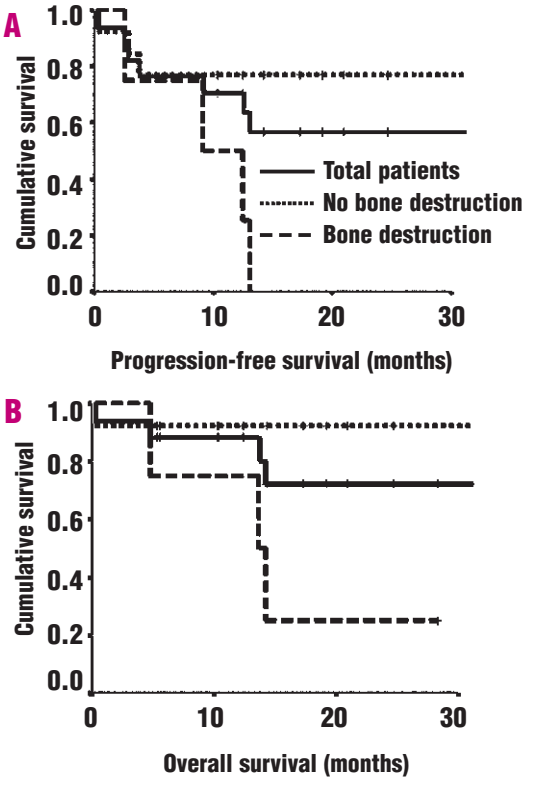

Figure 1. Progression-free and overall survival curves

pared with our previous study (four cycles of CHOP followed by IFRT),[5] although the current regimen might have improved the complete remission rate, it failed to improve survival. Analyzing the failure pattern, we found that our current treatment strategy reduced locoregional failure, but not systemic failure. Earlier administration of radiation therapy seems to reduce locoregional failure. However, initial DI-CHOP and CHOP consolidation did not affect the incidence of systemic failure. The higher proportion of systemic failures could have been caused by a higher proportion of patients with advanced primary disease. This study included four cases with bone destruction (including one case with intracranial extension), whereas the previous study had not included any cases with bone destruction.[5] The comparison between the two groups (those with no bone destruction and those with bone destruction) showed significant differences in progression-free survival and overall survival rates (Figure 1). Another study reported that patients with bony destructive primary lesions had a poorer prognosis.[9] The results of our current study show that anthracycline-based chemotherapy is suboptimal, even for localized, nasal NTCL and at the maximal dose intensity. Future studies should investigate more effective non-anthracycline chemotherapeutic agents such as ifosfamide and etoposide, combined with early administration of radiation.[10]

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Key words: nasal NK/T-cell lymphoma, DI-CHOP

Prepublished online on February 17, 2006. PII: 03906078_9147.

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