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Consolidation radiotherapy to bulky disease in aggressive NHL. First results of the NHL B-94 trial of the DSHNHL

Abstract The impact of radiotherapy in aggressive NHL is not well defined. In the NHL B-94 trial of the DSHNHL, an irradiation of bulky disease areas was done after completing 6 cycles of CHOP/CHOEP chemotherapy. In the entire patient group, including those patients with extranodal disease and those who did not receive the complete chemotherapy, bulky disease was a significant independent prognostic factor concerning recurrence-free survival (66.1% (no bulk) vs. 53.3% (bulk), p=0.0001). Out of 366 patients with nodal disease only and 6 cycles of chemotherapy according to the protocol, 84 of 91 patients with bulky disease were irradiated with 36 Gy. In this group of patients the prognostic impact of bulky disease could not be shown any longer (recurrence-free survival 77.3% (no bulk) vs. 74.1% (bulk). Localized radiotherapy of bulky disease areas may therefore have contributed to an improvement in outcome in this high-risk group.

Keywords Aggressive NHL, bulky disease, radiotherapy

Introduction

The role of radiotherapy in the treatment of high-grade non Hodgkin lymphoma is not well defined and is controversial. Treatment policy includes strategies with involved field irradiation or irradiation of bulky and/or extranodal disease only [2, 3, 5, 6, 7, 9]. In the protocol of the German High Grade NHL Study Group (DSHNHL), radiotherapy was added after chemotherapy in patients with bulky disease; radiation was optional in cases with extranodal involvement. The presented data analysis is for patients with bulky disease only who were treated in the NHL B-94 trial.

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Material and methods

According to the study design, patients with an initial tumor size larger than 7.5 cm were defined to have "bulky disease." According to the protocol, an irradiation to the area of bulky disease had to be given after 6 cycles of chemotherapy. Total dose was 36 Gy given in single fractions of 1.8-2 Gy 5 times per week. Target volume included the lymph node area of the initial bulk with a field size reduction to the post-chemotherapy tumor volume. Out of the total of 959 patients included in the study, 323 (33.9%) had bulky disease 170 of these had additional extranodal lymphoma; thus the incidence of bulky disease in patients without extranodal disease was 15.9% (153/959).

As the presented study considers patients with nodal disease only, we took a closer look at all patients without extranodal disease in the trial (513). To evaluate the impact of radiotherapy after chemotherapy, we analysed the group of 366 patients with nodal disease only who completed therapy according to the protocol with CR/CRr (CR group): of this group, 91 patients had bulky disease and 84 of these were treated with radiotherapy; 7 patients with bulky disease were not irradiated because of prior surgery.

Results

Overall relapse rate in the CR group was 71/366 (19.4%); 22.5% (16/71) had a relapse in the initial site only, 49.3% (35/71) relapsed in initial sites as well as in new sites; only 20/71 cases (28.1%) showed a relapse in initially uninvolved, new sites only. There was no major difference in the distribution of sites of relapse between patients with or without bulky disease or between stages I/II and III/IV.

Out of a total of 1205 analysed lymph node areas, 11.4% (137/1205) showed the criteria of bulky disease, 1068 had lymphomas <7.5 cm. Interestingly enough, there was no difference between the two groups concerning the relapse rates in the initially involved nodal areas (8.6% (no bulk) vs 8% (bulk)). Therefore, the risk of local recurrence in the irradiated group of patients with

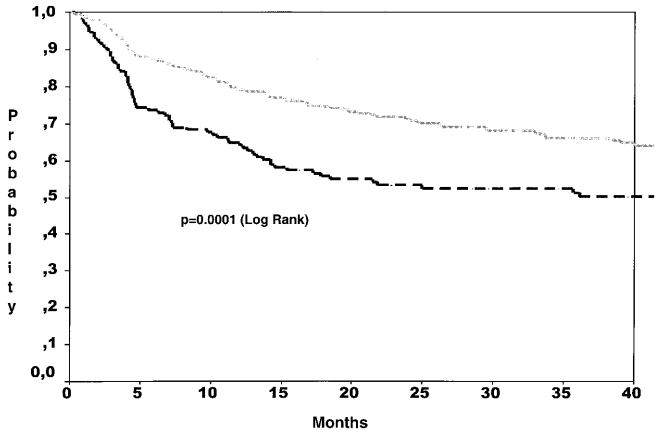

Fig. 1 Time to treatment failure for patients with nodal NHL (*n*=513): bulk (*n*=153, black curve) vs. no bulk (*n*=360, gray curve)

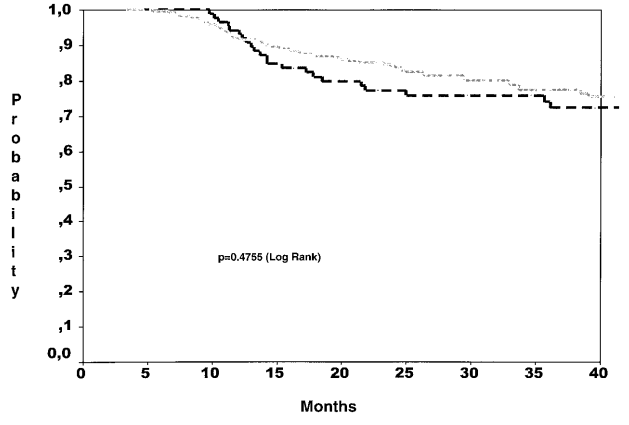

Fig. 2 Disease-free survival for patients with nodal NHL (*n*=366) after 6 cycles of chemotherapy plus radiotherapy in bulky disease: bulk (*n*= 91, black curve) vs. no bulk (*n*=275, gray curve)

bulky disease was as low as in the (unirradiated) group without bulky disease.

Regarding the whole group of patients with nodal disease (*n*=513), those with bulky disease had a significantly shorter time to treatment failure than those without bulky disease: three-year recurrence-free survival was 66.1% (no bulk) vs 53.3% (bulk), *p*=0.0001, (Fig. 1).

In contrast, there was no prognostic impact of initial bulky disease on recurrence-free survival for those patients who completed therapy according to the protocol including radiotherapy of bulky disease (*n*=366) (Fig. 2); in this group, patients with bulky disease had the same probability of 3 years relapse-free survival as those without (77.3% (no bulk) vs. 74.1% (bulk)). Additional radiotherapy therefore may have contributed to the fact that the risk factor "bulky disease" had no impact on recurrence-free survival in those patients who had received irradiation.

Conclusions

In addition to chemotherapy, radiotherapy is a well tolerated and effective treatment for aggressive NHL. There are two randomized phase III-trials that showed a significant improvement of results by including involved field radiotherapy compared to chemotherapy alone [4, 8]. Nevertheless, several current treatment protocols include radiotherapy only as an optional treatment modality in cases of bulky disease or residual lymphoma after chemotherapy [1, 10]. The DSHNHL concept specifies radiotherapy of 36 Gy to bulky disease after 6 cycles of chemotherapy. The fact that in those patients who received radiotherapy the prognostic factor "bulky disease" is no longer significant supports the data from the literature that radiotherapy is an effective consolidation treatment in patients with aggressive NHL.

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