Review

Current clinical trials for the treatment of adult Hodgkin’s disease: Common strategies and perspectives

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Summary
Strategies in the treatment of adult Hodgkin’s disease (HD) are changing strikingly in current clinical trials. In early as well as in intermediate stage HD a common aim of most study groups now is the reduction of radiation dose and volume in order to minimize severe late effects like myocardial damage and secondary neoplasias. As a consequence extended field irradiation is abandoned in nearly all trials, and combined modality treatment will be used not only in intermediate, but also in early stage HD. In advanced stage HD new chemotherapy regimens, based on the principle of a moderate dose escalation, for the first time seem to improve the therapeutic outcome. Thus, the priority in current clinical trials for advanced stage HD is the long-term evaluation of these new regimens with regard to treatment efficacy and toxicity.

Key words: clinical trials, dose intensification, extended field irradiation, Hodgkin’s disease

Introduction
The principles underlying stage-dependent treatment of Hodgkin’s disease (HD) are changing. In early stage HD extended field (EF) irradiation (without chemotherapy) has been the standard treatment for decades. Long-term survival (SV) rates of 90% and more were achieved. However, several studies have reported severe late effects of radiotherapy, e.g., myocardial infarction and a dramatically increased rate of secondary malignancies (SM), mostly solid cancers [1, 2]. As a consequence, most study groups now tend to substitute EF irradiation by involved field (IF) irradiation combined with chemotherapy. In intermediate stage HD, combined modality treatment (CMT), consisting of chemotherapy followed by EF irradiation, has been the standard, also leading to excellent cure rates of 80% to 90%. However, similar to the situation in early stage HD, EF irradiation in intermediate stage HD is a matter of critical discussion now in view of the severe late effects. Until recently in advanced stage HD disappointing long-term SV rates of about 50% could be achieved by eight to ten cycles of standard polychemotherapy (MOPP, COPP, ABVD) followed by additional radiotherapy to initial bulk tumors and/or residual masses. For the first time now, the poor prognosis of these patients seems to have improved by newly developed dose-intensified chemotherapy regimens such as BEACOPP or Stanford V. Current treatment strategies for advanced stage HD patients thus focus on the evaluation of these new regimens.

Current clinical trials

Early stage Hodgkin’s disease
Most study groups now focus on the reduction of radiotherapy (RT) dose or volume in the treatment of early stage HD, which includes disease stages I and II (based on the Ann Arbor Classification) without clinical risk factors. This goal might be achieved by reduction of the radiotherapy field size (EF vs. IF) and/or by reduction of the irradiation dose.

In order to reduce the irradiation volume, subtotal nodal irradiation (STNI) is compared with IF irradiation (30–36 Gy) combined with chemotherapy in clinical trials by the Stanford group (Stanford G1 trial: STNI vs. VBM × 6 plus IF), the South West Oncology Group (SWOG; STNI vs. ABVD × 3 plus IF), the European Organization for Research and Treatment of Cancer (EORTC; H7-F trial: STNI vs. EBVP × 6; H8-F trial: STNI vs. MOPP/ABV × 3) and the British National Lymphoma Investigation (BNLI; mantle-field irradiation vs. VAPEC-B plus IF). The value of the different chemotherapy regimens in the treatment of early stage HD is not yet clear.

In the HD7 trial of the German Hodgkin’s Lymphoma Study Group (GHSG) EF irradiation was compared with two cycles ABVD followed by IF irradiation. The trial was closed this year. A first interim analysis showed no differences for remission rates and disease-free survival (results not yet published). In the current HD10 trial, EF irradiation has been substituted in all treatment arms by IF irradiation. This trial focuses on the
number of chemotherapy cycles and the chemotherapy regimens themselves administered before radiotherapy as well as on dose reduction of the IF radiotherapy (ABVD × 2 plus 20 Gy IF vs. ABVD × 2 plus 30 Gy IF vs. ABVD × 4 plus 20 Gy IF vs. ABVD × 4 plus 30 Gy IF). Similarly, the EORTC, which has already shown that STNI can be substituted by chemotherapy (EBVP) plus IF irradiation, in the coming EORTC H9-F trial will test dose reduction in the IF after chemotherapy (EBVP × 6 plus 36 Gy IF vs. EBVP × 6 plus 20 Gy IF vs. EBVP × 6 without RT).

**Intermediate stage Hodgkin’s disease**

Due to the observation that certain clinical risk factors (RF) are associated with poor prognosis of stage I and II HD, most study groups have intensified treatment of these intermediate stage patients. The RF vary between different study groups and may include mediastinal mass, bulky disease, massive splenic disease, extranodal involvement, elevated erythrocyte sedimentation rate or anemia. Combined modality treatment (CMT) has been the standard treatment for these patients resulting in long-term SV rates of 80% to 90%. Nevertheless, in analogy to the discussion in early stage HD treatment, the question has now been raised whether intensity of irradiation can be reduced without compromising the excellent treatment results.

In the H8U trial the EORTC in cooperation with the French Adult Lymphoma Group (GELA) raised the question of the number of cycles of chemotherapy and of the irradiation volume (MOPP/ABV × 6 plus IF 36 Gy vs. MOPP/ABV × 4 plus IF 36 Gy vs. MOPP/ABV × 4 plus STNI). The trial has recently been closed. Results have not yet been published. However, in view of the coming H9U trial, the substitution of STNI with IF irradiation did not seem to significantly reduce treatment results. In all three treatment arms of the EORTC H9U trial, radiation therapy is given as IF irradiation with a dose of 30 Gy (ABVD × 6 plus IF vs. ABVD × 4 plus IF vs. BEACOPP × 4 plus IF). Two arms of this study are the same as those in the current HD11 trial by the GHSG. In HD11, IF has also been completely replaced by IF irradiation. This four-arm trial focuses on the chemotherapy regimen, the number of cycles administered before RT, and the radiation intensity (ABVD × 2 plus IF 20 Gy vs. ABVD × 2 plus IF 30 Gy vs. ABVD × 4 plus IF 20 Gy vs. ABVD × 4 plus IF 30 Gy).

Similarly, the North American study groups are currently testing reduction of radiotherapy intensity or, alternatively, have already abandoned EF irradiation. The Eastern Cooperative Oncology Group (ECOG) is launching a trial (E2496) in which exclusively initial bulky sites are irradiated (36 Gy) after chemotherapy with either six cycles of ABVD or three months of the Stanford V regimen. Whether radiotherapy is necessary at all in intermediate stage HD is tested in the National Cancer Institute of Canada (NCI-C) HD6 trial, which compares two cycles of ABVD plus EF irradiation (35 Gy) against four to six cycles of ABVD without radiotherapy. In this trial, however, patients with a large mediastinal mass or with bulky tumors >10 cm in diameter are excluded.

**Advanced stage Hodgkin’s disease**

Despite complete remission (CR) rates of more than 80% after six to eight cycles of standard polychemotherapy, such as MOPP, COPP or ABVD, the long-term SV of about 50% has remained disappointing in patients with advanced stage HD (Ann Arbor stages IIIB, IV). Several modifications of the standard chemotherapy regimens have been evaluated, e.g., MOPP alternating with ABVD, MOPP/ABV hybrid or COPP/ABV/IMEP. Until recently, however, neither modifications of the standard regimens nor any alternative regimen have been reported to improve SV of these patients [3, 4].

For instance, in the CALGB 8952 trial patients with stage III–IV HD or recurrent disease after RT were randomized between ABVD and MOPP/ABV (minimum of 8 cycles, maximum of 10 cycles, depending on response). This study was closed in 1995 based on excess of treatment related deaths and secondary neoplasias after treatment with the hybrid regimen. In an interim analysis in 1997 no significant differences in response rates and SV were reported for both treatment arms [5].

Not all of these studies, however, have been evaluated finally so far. For instance, the H34 trial of the EORTC lymphoma cooperative group started in 1989 and is still testing the MOPP/ABV hybrid in a response-adapted design. Patients with a CR after 4 × MOPP/ABV are treated with another two cycles of MOPP/ABV and then randomized between IF irradiation and no further therapy. Patients with a PR after 4 × MOPP/ABV also receive two further cycles and are then treated dependent on the results of evaluation. In case of CR, two further cycles MOPP/ABV are followed by randomization between IF irradiation and no further therapy; in case of PR, IF irradiation is given. The results of this study have not yet been published.

The MOPP/ABV hybrid has also been tested by the GELA. In the H89 GELA study for stage IIIB–IV HD patients MOPP/ABV is compared with ABVPP (six cycles of each regimen) followed by a comparison of two further cycles of chemotherapy vs. STNI. This study was closed in December 1996. A first interim analysis of this study was presented in 1995 showing high CR (85%) and SV (86%) rates (median follow-up 26 months) [6]. Further interim analyses have not yet been published. Thus, similar to the H34 trial, the value of the MOPP/ABV hybrid with regard to long-term SV cannot be defined as of yet.

In a joint study with the EBMT the GELA is now performing a randomized trial of high-dose therapy and autologous stem-cell transplantation versus conventional therapy for patients with advanced HD responding to first-line therapy using ABVD or an ABVD-like regimen (H96-1 protocol).
The BNLI in a collaboration with the Central Lymphoma group randomized the PABLOE regimen against an alternating administration of CHL/VPP and PABLOE. Significantly better disease-free survival rates after four years of follow-up were reported for the alternating regimen. The study is now closed. It might be concluded, that the inclusion of etoposide in chemotherapy regimens (like PABLOE) only improves the treatment results when combined with alkylating agents. However, long-term follow-up results are needed to allow any definite conclusion about the value of CHL/VPP/PABLOE. In order to further optimize treatment of advanced stage HD, the BNLI has now opened two studies in which patients are randomized either between ABVD and Stanford V (see below) or for ABVD and CHL/VPP/PABLOE-CHL/VPP/EVA.

Based on a mathematical model of tumor growth and chemotherapy sensitivity the GHSG has developed the BEACOPP regimen. The main principles of BEACOPP are: (1) increase of total dose, (2) acceleration of the administration schedule and (3) addition of a new drug. The BEACOPP regimen contains the main substances of COPP/ABVD (without vinblastine and dacarbazine) and, as an addition, etoposide. Cyclophosphamide, doxorubicin and etoposide are given within the first three days, the time interval between the courses has been shortened. Thus, the total duration of therapy, i.e., of eight cycles BEACOPP, is 24 weeks compared to 32 weeks for four double cycles COPP/ABVD [7]. In the HD9 trial by the GHSG, the standard COPP/ABVD chemotherapy was compared with BEACOPP in a baseline version and in an escalated version with dose escalation of cyclophosphamide, doxorubicin and etoposide. In this version, the use of G-CSF was mandatory. In the first interim analysis in 1996, the COPP/ABVD arm was shown to result in significantly worse treatment outcome and had to be closed (FETTF at 24 months 74% for COPP/ABVD vs. 85% for the pooled BEACOPP arms). The rate of patients with fatal progressive disease was reduced from 12% to 6% [8]. The interim analysis from 1998 confirms these results and additionally indicates superiority of BEACOPP escalated compared to BEACOPP baseline. Although the hematotoxicity of BEACOPP is significantly enhanced compared to COPP/ABVD, no significant differences in severe infections and treatment-related deaths were observed.

An approach comparable to BEACOPP baseline for dose intensification by treatment acceleration has been chosen by the Stanford group. In the Stanford V protocol the substances of MOPP/ABVD are used without procarbazine and dacarbazine, etoposide has been added as a new substance, and the duration of the chemotherapy has been shortened (12 weeks compared to six months for MOPP/ABVD). No results of randomized trials are available yet for this new protocol, which has been revealed to be superior to MOPP/ABVD in a single-center matched pair analysis of patients with stage IIIB–IV HD [9, 10].

The GELA is also currently testing a dose-intensified regimen in advanced stage HD. In a pilot study (H98-2) patients with maximally two risk factors receive a weekly regimen, the dose intensification of which is based on reduction of the duration of treatment and moderate dose escalation of doxorubicin [11].

Conclusions

Current clinical trials for the treatment of HD in Europe and North America share common strategies. Despite excellent treatment results, the role of radiotherapy in early and intermediate stage HD is questioned fundamentally. Based on numerous reports on severe late effects of radiotherapy, especially the high rate of second solid cancers, EF irradiation has been abandoned by most study groups. Instead, IF irradiation is administered and dose reduction in the IF is tested. As a consequence, the treatment strategies for early and intermediate stage HD are now similar, i.e., combined modality treatment is the treatment of choice for both patient groups. In early stage HD mild chemotherapy before RT is expected to avoid the high relapse rate after exclusive RT. In addition, this strategy should allow reduction of RT intensity without worsening the treatment outcome. In intermediate stage HD as well, an effective chemotherapy has to be defined which allows reduction of RT intensity without compromising the treatment results. In advanced stage HD after a long time of disappointing treatment results, perhaps a therapeutic breakthrough has been achieved with the development of dose-intensified regimens based on the concept of moderate dose escalation. The challenge now will be to hold the balance between treatment efficacy and late toxicity.

References

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