Hodgkin`s Diseases First Line Treatment

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Abstract

The German Hodgkin Study Group (GHSG) developed the BEACOPP regimen for further improving the outcome of patients with advanced Hodgkin's Lymphoma (HL). Since 1992, BEACOPP has been introduced in 3 different prospective randomised clinical trials of the GHSG to find an equilibrium between maximal efficacy and least toxicity with the BEACOPP- principle for the treatment of advanced stage HL.

The HD9 trial of the GHSG, compared the goldstandard at this time COP/ABVD (arm A) with the new BEACOPP principle in a standard setting (arm B) and in an escalated form (arm C).

The recent 10 year update of this trial shows the following results:

1196 of 1201 eligible, randomized patients were evaluable (260, 469 and 466 in arms A, B and C, respectively). The median follow-up times were 122, 111 and 107 months in arms A, B and C respectively (29-32 months longer than in 2004). 10-year FFTF rates in arms A, B and C were 64%, 70% and 82% respectively ($p<0.0001$). FFTF was significantly better in the increased-dose arm than in the standard-dose arm ($p<0.0001$). 10-year overall survival rates were 75%, 80% and 86% respectively ($p<0.001$). Overall survival was also significantly better in the increased-dose arm than in the standard-dose arm ($p=0.0053$). 74 second malignancies were documented as follows: 1, 7 and 14 acute myeloid leukemias (AML); 7, 8 and 5 non-Hodgkin lymphomas; 7, 16 and 9 solid tumors/others in arms A, B and C respectively. Kaplan-Meier estimates of 10-year AML cumulative incidences were 0.5%, 2.6% and 3.4% in arms A, B and C respectively ($p=0.032$).

These superior BEACOPP results are obtained inspite of a higher rate of secondary AML/MDS in the esc.BEACOPP arm. The number of toxic deaths during treatment, however, was lower for esc BEACOPP (1,6%) than for C/ABVD (1,8%) [1]

The majority of patients were treated in out- patient setting, in a multicenter study with more than 400 centers, including 120 private doctors, in Germany and 9 other European Countries.

To reduce acute and longterm toxicity, the GHSG started in the consecutive studies HD12 and HD15 for advanced stage HL to de- escalate BEACOPP by reducing the number of escalated BEACOPP cycles and by applying the baseline- dose- BEACOPP, a time dense regimen, called BEACOPP-14 .

The excellent results obtained with the BEACOPP principle challenge the seemingly global consensus that ABVD is the gold standard treatment strategy for advanced stage HL.

Introduction

Hodgkin Lymphoma (HL) is one of the best curable cancers of adulthood. In localized stages of the disease more than 95% of patients can be cured with modern treatment strategies. In advanced stages, comprising stages IIB with large mediastinal tumors and all stages III and IV according to the Ann Arbor classification, more than 85% of patients experience long term tumor free survival and in the current cohorts of HL survivors after 15 years more individuals have died due to adverse sequelaes of treatment than of Hodgkin related causes of death. Therefore current intentions for improvement aim for preserving the high cure rates while reducing the acute and long term toxicities. The definition of advanced HL varies considerably between different study groups and makes inter-study comparisons difficult.

BEACOPP in advanced stage HL

Development and results of the three BEACOPP regimens: baseline, escalated and BEACOPP –14.

HL is a very chemo-radio-sensitive disease, the pathognomonic Reed- Sterberg cell is extremely fragile upon in vitro manipulation, the primary tumor lesion consists of less than 0,1-1,0% tumor cells, the rest is reactive tissue. Hence, biologically this tumor should be responsive to a cytotoxic regimen using an optimal drug combination in an optimal time schedule and drug dosage to yield the highest tumor cell kill. Having made this

statement, it becomes obvious that the outcome of patients with advanced HL treated in most North-American or European multicenter studies with the common conventional strategies like ABVD, MOPP/ABVD or MOPP/ABV-hybrid yield suboptimal outcome results: for ABVD at 5 years FFS was 63% and OS was 82% [2].

To improve the outcome of patients with advanced stage HL one either should use new, effective drugs, however, these are not available,- or apply the existing drugs (-combinations) in a more suitable way to increase drug- intensity and drug- density.

The GHSG, in a model design on the basis of data from previous trials with the COPP/ABVD regimen, hypothesized that shortening the treatment interval would lead to a modest benefit. In 1992 the GHSG developed the BEACOPP regimen that is administered every 21 days on the basis of the COPP/ABVD alternating regime, which is administered every 28 days.. Baseline- BEACOPP is based on the same drug composition as the standard COPP/ABVD, but excludes vinblastine and dacarbazine, and adds etoposide. The dose for the baseline schedule is equivalent to COPP/ABVD.

The model further suggested that an escalation of dosage by 30% might intensify the cell kill by 10-15% [3]

In the resulting escalated BEACOPP- regimen the doses of cyclophosphamide, adriamycin, and etoposide are increased with G-CSF support.

After getting encouraging results in pilot studies [4, 5], the three-armed HD9 trial compared the escalated and the baseline BEACOPP regimen with the standard COPP/ABVD for the treatment of advanced-stage HL patients [6].

After a median observation time of 7 years, the superiority of the dose-escalated BEACOPP regimen was clearly demonstrated in terms of FFTF (BEACOPP esc.: 85%, BEACOPP baseline: 75%, COPP/ABVD: 67%) and OS (BEACOPP esc.: 90%, BEACOPP baseline: 84%, COPP/ABVD: 79%) [1]. There was a higher number of secondary AML/MDS in the escalated BEACOPP arm (n=11) compared with the C/ABVD arm (n= 1), the death rate due to treatment induced toxicity was lower in the esc.BEACOPP arm (1,6% vs 1,8%). Death due to progressive HL was 1,7% for esc BEACOPP and 8,7% for C/ABVD.

Decreasing toxicity by reducing the number of escalated BEACOPP cycles and using the baseline BEACOPP-14 regimen: preliminary results of the completed HD12- and ongoing HD15- studies

Taking in account the high chemo- and radiosensitivity of the fragile Reed- Sterberg cells and a very pronounced genetic lability of the tumor cells leading to early secondary resistance, it seems of outmost importance to get a maximal and rapid cell kill at the onset of therapy, possibly in the first two months after commencing treatment. Recent studies, using the PET as a predictor of response, show that an early CR is the most favorable prognostic indicator.

In North American and European multicenter studies using the conventional ABVD, MOPP/ABV etc., this aim was hardly reached when 10-15% of the patients had refractory tumors and progressed and 30-35% relapsed within 5 years, resulting in an OS rate of 70-80% at 5-10 years. The data with the escalated BEACOPP regime, however, after 7 years mot for FFS are 85% and for OS 90%, while 99% of the AML/MDS occurred after 1-5 years, none was observed in the last two years.

Modern therapeutic strategies aim at both: reducing therapy-induced late toxicities while maintaining effective tumour control.

Therefore, in the subsequent HD12 trial of the GHSG, chemotherapy was de-escalated by comparing eight cycles of escalated BEACOPP with four escalated and four baseline cycles, with or without consolidating radiation to initial bulky and residual disease. The results are very promising and absolutely in line with the HD9 results:

After a median follow-up of 2 years, FFTF and OS for the whole cohort were 88% and 94%, respectively. For the group getting 4escalated BEACOPP+ 4 baseline BEACOPP, FFTF was 88% and OS 94% respectively; For the patient cohort getting 8 esc BEACOPP, FFTF was 90% and OS: 96%.

In this HD-12 study less than 35% of the total cohort of patients received consolidative involved field radiation. The rate of secondary AML/MDS was at the same time point of observation only half of that in the HD-9 study .

The currently ongoing HD15 trial for the treatment of advanced-stage HL compares 8 courses of escalated BEACOPP with 6 courses of escalated BEACOPP or 8 courses of the baseline BEACOPP-14 to further reduce toxicity. As an example for

a time dense/ intensified chemotherapy, the BEACOPP-14 schedule, representing a BEACOPP-baseline variant given in 14 day intervals, was developed .

Consolidative radiaton was given to 65% of patients. This regimen was tested in a multicenter pilot study with the final analysis showing an estimated FFTF of 90%, an OS of 95% at 5 years median observation time . The acute hematotoxicity was significantly reduced and ranged between that of escalated and baseline BEACOPP-21 [7]. In this pilot study with 94 patients after 5 years mot there was no AML/MDS, no solid tumor, only 1 NHL as secondary neoplasia. There were two toxic deaths during treatment.

Conclusion and future aims

The question is relevant

Is it justified to call ABVD the goldstandard treatment strategy for advanced stage HL patients?

The answer might be yes, if one takes the recent data of North American single center studies (Vancouver) in account, where 25-30% of patients with stages I-II with bulky tumors and B-symptoms are subsummized into the group of advanced stage HL patients. These patients, however, are treated in the GHSG in the early unfavorable (intermediate) cohort with just 4 cycles of ABVD+ 20 Gy IF-RT, resulting in a 5 year FFS of 90% and an OS rate of 97%!

The robust data from the North American multicenter studies (CALGB, ECOG, Intergroup) including only stages III-IV and possibly the IIB patients with large mediastinal masses in the advanced stage group showed rather disappointing results with a 10 year FFS of 50% [8].

The answer might be no, if one accepts that at a median observation time of 7 years the GHSG data with escalated BEACOPP (HD9- study) [6, 1] showed that 11 more young patients (median age 28 years) out of a group of 100 escalated BEACOPP treated patients are alive and possibly cured, compared with the group of C/ABVD treated patients, where 21 patients had already died at this time point.

The pivotal question is

How much long term toxicity do we expect for escalated BEACOPP treated patients after 10, 15 and 20 years follow up? There is certainly no answer to this question at the moment. The 10 year data of the HD9 study, however, look promising and inspite of a higher number of initially occuring AML/MDS there is a significant superiority for the escalated BEACOPP regimen compared to C/ABVD and 11 more young patients survive with this admittedly very toxic principle than with the ABVD regime in a multi center study with more than 500 participating centers and many patients treated in outpatient setting, as it is the case in the GHSG.

The difference for freedom from treatment failure (FFTF) at 10 years is even higher in the two arms: 64% for C/ABVD and 82% for BEACOPP escalated. That means 18% of patients treated with BEACOPP escalated do not need a salvage treatment conferring a even higer risk of AML/MDS than BEACOPP escalated when high dose chemotherapy with autologous stem cell support is given as salvage.

To further reduce the danger of late complications, like secondary tumors, cardiac and pulmonary late toxicities, the GHSG aims at reducing the number of escalated BEACOPP cycles from a total of 8 to 6 (HD15) and in the HD12 trial even to 4 escalated BEACOPP + 4 baseline BEACOPP cycles. Parallel to this de-escalation of BEACOPP the amount of radiotherapy is reduced from 65% of patients receiving consolidating radiation in the HD9 trial to less than 5% in the HD15 trial, where involved field RT is only given to PET positive >2,5cm rest tumors. All PET negative rest tumors, irrespective of their size after 6 or 8 escalated BEACOPP- or 8 BEACOPP-14- cycles, do not get IF-RT anymore!

The future strategies for advanced HL are 2 fold:

1. risk adapted therapy allocating the patients according to their risk of being resistant or relapsing using the International Prognostic Score (Hasenclever/Diehl) and treating patients with the lower risk IPS 0-2 with ABVD and with the higher risk IPS > 3 with BEACOPP escalated and

2. response adapted therapy using FDG-PET as a response- and prognosis predictor. That means, after 2 courses of either ABVD or BEACOPP esc and a negative PET: continue with ABVD, if PET is positive, change to BEACOPP esc.

The ultimate answer to the question whether escalated BEACOPP is superior to ABVD only can be answered in a randomized multi center, multi culture setting, testing both regimen with and without radiation and in the different strata of the risk groups of the International Prognostic Factor Project [9]. A global study, lead by the EORTC is currently being undertaken in North America, Canada, Australia and in Europe (EORTC (#20012) [10].

References

1. Diehl V, Brillant C, Franklin J, et al. BEACOPP chemotherapy for Advanced Hodgkin's Disease: Results of Further Analyses of the HD9- and HD12- Trials of the German Hodgkin Study Group (GHSG). Blood 2004 Nov 16; 104(11)A: 307.
2. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol. 2003 Feb 15;21(4):607-14.
3. Loeffler M, Hasenclever D, Diehl V Model based development of the BEACOPP regimen for advanced stage Hodgkin's disease. German Hodgkin's Lymphoma Study Group. Ann Oncol. 1998;9 Suppl 5: S73-8.
4. Diehl V. Dose-escalation study for the treatment of Hodgkin's disease. The German Hodgkin Study Group (GHSG). Ann Hematol 1993; 66: p139-140.
5. Diehl V, Sieber M, Ruffer U, et al. BEACOPP: an intensified chemotherapy regimen in advanced Hodgkin's disease. The German Hodgkin's Lymphoma Study Group. Ann Oncol 1997; 8:143-148.
6. Diehl V, Franklin J, Pfreundschuh M, et al., Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003 Jun 12;348(24):2386-95.
7. Sieber M, Bredenfeld H, Josting A, et al. 14-day variant of the bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone regimen in advanced-stage Hodgkin's lymphoma: results of a pilot study of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 2003 May 1;21(9):1734-9.
8. Canellos GP, Niedzwiecki D Long-term follow-up of Hodgkin's disease trial N Engl J Med. 2002 May 2;346(18):1417-8.
9. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med. 1998 Nov 19;339(21):1506-14.
10. Raemaekers J, Kluin-Nelemans H, Teodorovic I, et al. The achievements of the EORTC Lymphoma Group. European Organisation for Research and Treatment of Cancer. Eur J Cancer 38, Suppl 4: S107-S113, 2002.