Early Intensification Treatment Approach in Advanced-stage Hodgkin Lymphoma

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KEYWORDS

• Hodgkin lymphoma • BEACOPP • Overall survival • Evidence

KEY POINTS

- No significant or only relevant differences have been documented in randomized trials between ABVD and $BEACOPP_{escalated}$ with regard to acute treatment-related mortality, second solid tumors, second acute myeloid leukemia, or any other late toxicities. However, data from non-controlled studies suggest a more pronounced gonadal toxicity with $BEACOPP_{escalated}$.
- The patient's perspective on the importance of gonadal toxicity as compared with the importance of being cured must not be ignored. Also, the patient's perspective regarding the importance of not experiencing relapse from their malignant disease must not be ignored.
- Regarding antilymphoma efficacy, the 5-year progression-free survival for advanced-stage Hodgkin lymphoma patients up to 60 years old treated with $BEACOPP_{escalated}$ is approximately 90%. This is about 20% better than the results with ABVD.
- With 6 cycles of $BEACOPP_{escalated}$ as first-line treatment, overall survival at 5 years is 95%. This is 10% better than ABVD as initial treatment as confirmed in a meta-analysis providing highest level of evidence.
- Both physicians and patients must be aware of the meaningfully higher risk of death at 5 years already when using ABVD as first-line treatment. Whenever the health care setting allows administering $BEACOPP_{escalated}$, the progressionfree and overall survival benefit clearly advocate this intensified first-line treatment as standard of care.

INTRODUCTION

Hodgkin lymphoma (HL) is among the most common malignancies in young adults. Survival has substantially increased over the last decades, even for patients in the advanced stages. How to balance risks and benefits of different treatment strategies, however, still remains a matter of controversy. The key question is, should intensified chemotherapy be applied upfront or should it be reserved for relapsing patients.[1] The early intensification approach aims at curing as many patients as possible with

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an aggressive first-line chemotherapy.[2] This approach is standard of care in European HL study groups such as the German Hodgkin Study Group (GHSG), The Lymphoma Study Association, and the European Organisation for Research and Treatment of Cancer. Standard regimen is 6 cycles of $BEACOPP_{escalated}$ (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) followed by radiotherapy to metabolic active residual disease. This approach induces high progression-free and overall survival rates (PFS, OS), but exposes patients to considerable acute chemotherapy-related toxicity.[2] Because the discussion on its efficacy and toxicity profile as compared with initial treatment with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) has been and still is emotional and sometimes reflects more individual beliefs than currently available knowledge,[3–5] this article aims at summarizing the most important facts on $BEACOPP_{escalated}$ derived from randomized trials.

EFFICACY: PFS AND OS

HD9

$BEACOPP_{escalated}$ reflects the introduction of granulocyte-colonystimulating factor (G-CSF) in hematology. In the 1980s it was hypothesized that dose density might increase the response rate of chemotherapy-sensitive tumors. Dirk Hasenclever developed a statistical model of the association of tumor growth kinetics and the effects of chemotherapy. The model was used to simulate the effect of dose escalation, dose density, and schedule changes in the COPP/ABVD regimen. This simulation demonstrated that the most potent effect would be achieved through dose escalation of cytostatics. This effect was estimated at an increase of 10% to 15% in PFS after 5 years. From this model, the BEACOPP regimen with G-CSF support was developed and tested versus the former standard COPP/ABVD in the HD9 study.[2] The HD9 study randomized 1195 patients in 3 treatment groups (COPP/ABVD, $BEACOPP_{baseline}$, and $BEACOPP_{escalated}$) and clearly demonstrated the superiority of $BEACOPP_{escalated}$. The 10-year data for this study have confirmed the initial results: the freedom from treatment failure and OS rates for COPP/ABVD were 74% and 75%, respectively, after 120 months. The corresponding results for $BEACOPP_{escalated}$ are 82% and 86%, respectively.[6] OS is thus 11% better than with standard COPP/ABVD. This effect is particularly pronounced in the group of patients with an intermediate risk profile according to the international prognostic score (IPS 2-3), which also forms the largest subgroup of patients (IPS 0-1: 28%, IPS 2-3: 38%, IPS 4-7: 13%).

HD12

However, the toxicity of 8 cycles of $BEACOPP_{escalated}$ is high. In addition to the considerable acute toxicity, the development of secondary acute leukemia prompted concern. In the HD9 study, the incidence of secondary acute leukemia was 3% compared with only 0.4% in the COPP/ABVD arm. The follow-up study HD12 therefore looked at reducing the chemotherapy to 4 cycles of $BEACOPP_{escalated}$ followed by 4 cycles of $BEACOPP_{baseline}$ ("4+4" regimen).[7] At 5 years, there were no significant differences regarding OS or PFS, although there was a decrease in absolute numbers with the 4+4 regimen. Importantly, the incidence of severe toxicities could not be reduced by the reduction of chemotherapy, so 8 cycles of $BEACOPP_{escalated}$ remained standard of care in the GHSG.

HD15

In the subsequent study, de-escalation of chemotherapy was investigated with a reduction in the number of escalated cycles from 8 to 6 and with the introduction of