

Modifying therapy in patients with advanced Hodgkin's lymphoma by integrating early metabolic response by interim PET-CT

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Hodgkin's lymphoma shows an annual incidence of around 2-3 per 100,000 habitants in the Western hemisphere with a larger peak in younger adults between 20 and 30 years and a smaller peak in adults above 65 years. Although Hodgkin's lymphoma is rare within the general population (accounting for less than 1% of all de novo neoplasms occurring every year worldwide) (1), it belongs to the most frequent malignancies in young adults and represents the most frequent hematological malignancy in this age group (2). Outcomes of patients with Hodgkin's lymphoma in general are favorable, with the vast majority of patients achieving permanent cure by standard therapies. Survivors, however, may face the problems caused by late toxicities such as secondary tumors or cardiovascular complications.

Even patients with advanced Hodgkin's lymphoma can be successfully treated with a cure rate of up to 80% by chemotherapy regimens such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). The escalated BEACOPP regimen (bleomycin, vincristine, procarbazine, and prednisone combined with higher than standard doses of etoposide, doxorubicin, and cyclophosphamide) appears to result in even 5% to 10% higher 5-year survival rates as compared to ABVD according to a large and comprehensive meta-analysis (3). As an example, the German Hodgkin Study Group compared escalated BEACOPP versus standard BEACOPP versus ABVD alternating with COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) within the HD9 trial in a large cohort of 1,196 patients with advanced Hodgkin's lymphoma. The 10-year follow-up demonstrated a significantly higher freedom from treatment failure (FFTF) rate of

82% for escalated BEACOPP as compared to 70% in the standard BEACOPP and 64% in the ABVD/COPP arms ($P < 0.001$). Similarly, overall survival (OS) rates were 86% for escalated BEACOPP, 80% for standard BEACOPP and 75% for ABVD/COPP (4). These significantly improved OS and FFTF rates for patients with advanced Hodgkin's lymphoma were suggestive for improvement of the clinical outcomes by escalated BEACOPP.

Nevertheless, escalated BEACOPP therapy is associated with an increased risk of long-term hematologic as well as non-hematologic toxicities (4). Examples are persisting infertility and chronic fatigue. Additionally, survivors have a considerable risk for therapy-related myelodysplastic syndrome (t-MDS) or acute myeloid leukemia (t-AML) (5). Especially the combination of BEACOPP chemotherapy with irradiation is associated with an increased risk of solid tumors (6). Considering the long life expectancy of patients with Hodgkin's lymphoma nowadays and the rather young age of many affected individuals, these long-term side effects of escalated BEACOPP therapy deserve attention. ABVD has lower rates of adverse-event rates as compared to escalated BEACOPP, but shows a relevant pulmonary toxic potential due to the use of bleomycin (5). Martin *et al.* investigated 140 patients with Hodgkin's lymphoma who were treated with bleomycin-containing chemotherapy regimens. Bleomycin pulmonary toxicity that was defined by pulmonary symptoms, bilateral interstitial infiltrates, and absence of evident infectious etiology was documented in 18% of the patients. Patients with bleomycin pulmonary toxicity had a significantly lower median 5-year OS rate of 63% as compared to 90% in the patients without ($P = 0.001$)

and a high mortality rate of 24% (7). The frequency of pulmonary toxicity by bleomycin increases with higher age (7) and with consolidation thoracic radiotherapy. Consolidation radiotherapy typically is administered e.g., in case of bulk lymphadenopathy at first manifestation or for residual lymphoma manifestations at the end of chemotherapy.

Since more intensive regimens trade little overall survival benefits with significant toxicity, there is an obvious need for better predictive diagnostic tools which help to avoid overtreatment of patients. Positron emission tomography (PET)-computed tomography (CT) with 18F-fluorescein di- β -D-galactopyranoside (18F-FDG) could be one such tool that may allow to estimate at an early time point response to treatment and tailor subsequent treatment intensity. At the 11th International Conference on Malignant Lymphoma in Lugano (focusing on Non-Hodgkin and Hodgkin's lymphomas) in 2011, FDG PET-CT was formally incorporated into standard staging for FDG-avid non-Hodgkin's and Hodgkin's lymphomas (8). According to the Deauville Criteria (9) a five point scoring system is used for the analysis of PET-CT scan at diagnosis and during the course of treatment. These criteria are based on the visual interpretation of the FDG-uptake which is related to the mediastinum (corresponding to the blood pool) and the liver. The highest scoring value of five refers to a markedly increased uptake higher than liver or any new lesions (on response evaluation), the lowest scoring value of one refers to no uptake above background. For DLBCL, PET is considered appropriate for staging and baseline PET parameters such as metabolic tumor volume were determined to be prognostically relevant. Early complete metabolic response (CMR) is predictive of CMR at the end of treatment with excellent prognosis (10). Recently, Press *et al.* published an intergroup trial including an early FDG-PET analysis after the first two cycles of ABVD chemotherapy in patients with stage III-IV Hodgkin's lymphoma. Patients with a negative PET result received an additional four cycles of ABVD, whereas those with positive results were switched to six cycles of escalated BEACOPP. Within the subgroup of patients being PET-positive, the 2-year estimate for PFS was 64% which was rather favorable considering the adverse features of the respective patient subgroup. This allowed the conclusion that early metabolic response adapted therapy is promising for patients with advanced Hodgkin's lymphoma (11). An Italian-Danish prospective trial suggested that an early FDG-PET scan even overshadows the prognostic impact of the international

prognostic score (IPS) in patients with advanced Hodgkin's lymphoma. By multivariate analysis, only the PET-2 results maintained significance whereas all other parameters that were prognostically relevant by univariate analysis lost significance (12). In the HD15 trial, Engert *et al.* reported a negative predictive value for lymphoma recurrence at 12 months of 94.1% for PET performed after termination of BEACOPP therapy (either 8x escalated BEACOPP, 6x escalated BEACOPP, or 8x BEACOPP-14) in patients with advanced Hodgkin's lymphoma. PET done after the end of chemotherapy was found able to guide the decision on additional radiotherapy (13).

In June 2016, Johnson *et al.* published their study "Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma" in the *New England Journal of Medicine* (14). Within a prospective multicenter international approach, the authors evaluated the potential of PET-CT for early measurement of the response to chemotherapy in patients with advanced Hodgkin's lymphoma. The authors performed either de-escalation or intensification of therapy according to the results of the PET-CT scan during the early course of therapy. A total of 1,214 adult patients (≥ 18 years) with newly diagnosed advanced classic Hodgkin's lymphoma (stage IIB-IV, or stage IIA with adverse features such as bulky disease or ≥ 3 involved sites) were registered in the period 2008-2012. Median age of the patients was 33 years with an upper range of 79 years. More than 130 centers from UK, Italy, Australia, New Zealand, and Scandinavian countries were participating in the study.

Following a baseline PET-CT scan at initial diagnosis, two cycles of ABVD chemotherapy were applied followed by an interim PET-CT scan. Imaging was centrally reviewed by two investigators from different core laboratories (who could consult a third investigator in case of diverging results). A 5-point scale was used for categorization of the PET results. In patients with negative results according to the interim PET-CT analysis (PET score 1-3) after the first two ABVD cycles, randomization was performed to either receive cycles 3-6 as ABVD ("ABVD group", including bleomycin) or AVD therapy ("AVD group", without bleomycin). These patients with negative results at the interim PET-CT would not undergo consolidation radiotherapy within the further follow-up. In case the PET-CT scan showed positive results (PET score 4-5), therapy was continued with BEACOPP (either escalated BEACOPP or BEACOPP-14). These patients with positive results at the interim PET-CT were scheduled for a third PET-

CT during further follow-up. In case of positive findings at the third PET-CT patients would undergo salvage therapy following local protocols.

More than 83% of the patients had negative findings in the first interim PET-CT and could be randomized within the ABVD and AVD arms regarding the subsequent chemotherapy courses. With a median follow-up of 41 months, the 3-year progression-free survival rate in the ABVD group was 85.7% as compared to 84.4% in the AVD group; the OS rates were 97.2% vs. 97.6%. Thus, the results of both strategies (treatment continuation with bleomycin versus omission of bleomycin) were very similar in the PET-negative patients. The risk of treatment failure due to omission of bleomycin within the first chemotherapy cycles was minimal with 1.6% in the study (14). Patients in the AVD group (without bleomycin) showed a lower incidence of pulmonary complications as compared to the ABVD group (including bleomycin).

The patients receiving the BEACOPP regimens due to positive findings at the interim PET-CT scan achieved negative findings in 74.4% on a third PET-CT scan, a 3-year PFS rate of 67.5% and an OS rate of 87.8%. Escalated BEACOPP and BEACOPP-14 showed no significant differences with regards to clinical results and toxicity. Differences were only seen with regards to higher frequencies of thrombocytopenia and febrile neutropenia in the patients with escalated BEACOPP as compared to those with BEACOPP-14 (14).

Thus, the novel strategy performing de-escalation of therapy by omitting bleomycin in case there was a high probability of cure after initial ABVD therapy but therapy intensification for patients at a higher risk of treatment failure (in whom the risks of additional therapy were justified) seemed successful. Only 6.5% of patients finally underwent radiotherapy in the study. This was much less than in previous studies with 30–60% of patients with advanced Hodgkin's lymphoma receiving radiotherapy (14). The results of patients with positive results upon interim PET-CT analysis that were subsequently transferred to BEACOPP were acceptable since the 3-year PFS rate was 67.5% in this adverse subgroup (14).

Future prospective studies should clarify additional questions, e.g., whether the predictive value may be improved by earlier performance of the PET-CT scan after only one cycle (14). Hutchings *et al.* investigated a cohort of 126 patients with Hodgkin's lymphoma after one chemotherapy cycle by PET-CT (PET-1). The majority were additionally evaluated after the second cycle (PET-2). PET-CT scans

were independently analyzed by two blinded reviewers using a five-point scale. The prognostic value of PET1 was statistically significant with respect to PFS and OS. The 2-year PFS for PET1-negative patients was 94.1% as compared to 40.8% for the PET1-positive patients. No patient who achieved negative results by the first PET-CT analysis was positive in the second PET-CT analysis. Therefore, the authors considered that PET-CT at a very early time point after one cycle of chemotherapy only is a strong prognostic parameter in patients with Hodgkin's lymphoma (15). Early PET-CT analyses evaluating the metabolic response may also be investigated for use in patients with relapsed or refractory Hodgkin's lymphoma, eventually also for those receiving therapies such as the antibody-drug conjugate brentuximab vedotin (16) or the PD-1-blocking antibody nivolumab (17).

In conclusion, Johnson *et al.* (14) were able to confirm that rapid metabolic response indicated by an early interim PET-CT allows performing de-escalation or intensification of therapy in patients with Hodgkin's lymphoma. Considering the expanding arsenal of therapeutic agents for patients with Hodgkin's lymphoma (e.g., PD-1 inhibitors or brentuximab vedotin) the need for valid diagnostic tools to monitor the response of patients in the early treatment phase will even grow in the near future. The study from Johnson *et al.* (14) contributes to integrating early metabolic response into therapeutic planning and represents a further step towards more individualized therapeutic strategies in the challenging subgroup of patients with advanced Hodgkin's lymphoma.

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Footnote

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