Treatment of Hodgkin's lymphoma in childhood and adolescence without radiotherapy

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Response to the editorials from Carella, Corazzelli and Vassilakopoulos *et al.*

We appreciate the well balanced commentaries on the final results of the GPOH-HD95 trial (1) and thank the experts for their positive and encouraging judgment as well as for important critical comments and ideas regarding the further improvement of treatment in Hodgkin lymphoma (HL) of childhood and adolescence (2-4). We also thank the editor of the *Journal* for giving us the opportunity to respond to these constructive statements.

The three authors independently confirm the importance of the evidence that radiotherapy (RT) can be omitted at least in a subset of patients with HL as has been shown in the GPOH-HD95 trial for early stage disease when chemotherapy alone had induced a strictly defined and controlled complete remission (CR). This approach to omit RT has been tried by several groups around the globe in countries with limited financial resources, as well, as in highly industrialized countries (5-11).

We also completely agree with the statement that the recommendation to omit radiotherapy in early stage HL patients achieving a CR after chemotherapy can so far only be given to patients stratified according to the DAL/GPOH tradition who were treated with two cycles of the very potent chemotherapy regimen OPPA or OEPA, and who also had a central evaluation of all imaging results by an experienced reference trial coordination center before and during treatment. To our impression and experience this strategy represents the most important result of this trial and can be offered as well in countries with limited economic resources when functional imaging is not available.

Vassilakopoulos *et al.* (4) discuss that the definition of CR despite persisting residuals of <2 mL could have caused relapses, especially in patients of intermediate and advanced stages, since such lesions may contain viable tumor. He and Corazzelli (3) emphasize that with risk- and response-adapted strategies the proportion of patients treated without RT could be further increased by using functional imaging aiming to better discriminate patients with residual morphological remnants from those with still active residual lymphoma. We also are convinced that an early response evaluation with [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) following one or two cycles of front-line chemotherapy will probably be the best way to identify patients who can be cured by chemotherapy alone. Many study groups around the world presently explore such a strategy.

Vassilakopoulos *et al.* (4) also stress the high 10-year overall survival (OS) rates in the trial GPOH-HD95 for the group of non-irradiated patients in intermediate (98%) and advanced (100%) stages. They conclude and thereby confirm our experience that patients without prior irradiation apparently can be successfully salvaged after relapse (12). However, we do not recommend risking more relapses by a weaker front-line therapy since late effects will probably increase due to the intensified salvage therapy using more chemotherapy and radiation, in many cases amplified by additional high-dose chemotherapy with subsequent autologous stem cell transplantation.

The three commentaries also acknowledge that it was safe to reduce the consolidating RT dose from 25 Gy in early and intermediate stages (as used in DAL-HD90) to

20 Gy in GPOH-HD95. Corazelli (3), however, raises concern that this may not ultimately lessen post-actinic sequelae. We agree that we do not know whether the effect of this dose reduction will reduce adverse late effects like secondary malignant neoplasms to a greater extent but we assume that at least some consequences such as local growth disturbances and radiogenic cardiovascular damages will decrease with lower RT doses. This was demonstrated in a recently published study on cardiac late effects following mediastinal RT (13). Radiotherapy will certainly continue to have a role in treating pediatric HL but indications for its use have to be defined clearly and modern treatment techniques will allow even better shielding of normal tissue.

Careful efforts will be needed to optimize the balance between cure and diminishing late effects in the treatment of pediatric HL. The authors hope that the GPOH-HD95 trial outcome could contribute to the ambitious goal of tailored treatment for HL especially in children and adolescents.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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