Omitting or reducing radiotherapy in childhood or adolescence Hodgkin Lymphoma

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Abstract: Despite high cure rates, treatment of childhood Hodgkin Lymphoma (HL) is associated with late effects caused mainly by radiotherapy (RT). In the GPOH-HD95 trial of the German Society of Pediatric Oncology and Hematology that was recently published in the *Journal of Clinical Oncology*, RT was spared in patients achieving a stringently defined complete remission (CR) with chemotherapy and reduced in patients with a good partial remission (PR). Overall, RT-treated patients had superior PFS, but overall survival (OS) was almost identical within each risk-stratified treatment group irrespectively of the use of RT. In the low-risk group, RT could be safely omitted in 20% of patients. In contrast, failure rates were considered unacceptable, when RT was omitted in intermediate or high risk patients achieving a CR. However, salvage therapy was successful, equalizing overall survival between irradiated and non-irradiated patients. Although GPOH-HD95 points out to the omission of RT in selected patients achieving a CR after chemotherapy, especially those in the low-risk group, more than 80% of the patients are still irradiated. Notably, the GPOH-HD95 was not a randomized trial. In conclusion, according to the GPOH-HD95 trial, RT can be safely omitted in pediatric and adolescent patients with low-risk, early stage HL achieving a stringently defined CR after 2 cycles of OPPA or OEPA chemotherapy. RT dose could also be reduced in case of good PR by conventional imaging. However, conventional response assessment is not the optimal means to decide whether RT is needed or not. It is now increasingly recognized that RT can be omitted in many patients with HL without compromising the final outcome and it appears wise to try to stringently limit RT in those patients who really need it. This might be achieved through the use of modern functional imaging (PET/CT). Such efforts are already in progress and results regarding efficacy are awaited relatively soon.

Keywords: Hodgkin Lymphoma (HL); childhood; adolescents; radiotherapy (RT); chemotherapy

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The outcome of patients with Hodgkin Lymphoma (HL) has improved greatly over the last decades so that the disease is considered curable in the majority of patients (1,2). The continuous improvement in cure rates has emphasized the importance of long-term treatment-related toxicities, caused mainly by radiotherapy (RT), including secondary malignant neoplasms (SMNs), cardiac and pulmonary toxicity, infertility, and thyroid disorders (2,3). Current treatment approach in adult HL generally includes anthracycline-based chemotherapy with involved-field radiotherapy (IF-RT) in the limited stages of the disease and similar (but longer) or more intensive chemotherapy (alone or with RT) in the advanced stages. Childhood HL represents 9% of all pediatric malignancies and has an even more favorable prognosis than its adult counterpart, with 5-year survival rate exceeding 95% (2). Since the long-term effects of RT are more prominent in children and adolescents, the issue of omission of RT becomes of paramount importance in

this patient population.

This commentary refers to a recent article published in the *Journal of Clinical Oncology*, reporting on the results of the GPOH-HD95 trial of the German Society of Pediatric Oncology and Hematology (4). The trial aimed to investigate whether reduction of RT in children and adolescents with HL would permit to maintain the high cure rates, in an effort to minimize the risk of late side effects. More specifically, RT was omitted in case of "complete remission" (CR) after chemotherapy, while RT dose was reduced from 25 to 20 Gy in patients with "good partial remissions" (good PRs). GPOH-HD95 was not a randomized trial and also took into account historical comparisons with the previous DAL-HD-90 trial (5).

In the above mentioned article (4), 925 pediatric or adolescent patients with classical Hodgkin Lymphoma (cHL) were divided in three treatment groups (TG1: early stages—i.e., IA/B, IIA; TG2: intermediate stages—i.e., I/IIA$_E$, IIB, IIIA; TG3: advanced stages—i.e., IIB$_E$, IIIA/B$_E$, IIIB, IVA/B), based on Ann Arbor classification, the presence of B-symptoms and/or extranodal disease. All patients received 2 cycles of OPPA or OEPA (according to gender and stage); TG2 and TG3 patients received 2 or 4 additional cycles of COPP respectively. RT was omitted in patients achieving CR, defined as a >95% reduction of tumor volume with <2 mL residuals in all previously involved regions. If CR was not achieved, patients received reduced involved field RT (RIF-RT) at doses depended on the degree of response in every region: In regions with good PR, defined as >75% reduction of tumor volume, RT dose was reduced to 20 Gy compared with 25 Gy in previous studies; regions with <75% reduction in tumor volume received 30 Gy and those with >50 mL residuals received 35 Gy. Extranodal sites were treated individually with specific guidelines. Notably, this stratification did not take account the presence of other risk factors used by other study groups, particularly the presence of bulky disease (6).

The results of this trial confirmed the favorable outcome of HL in pediatric and adolescent patients with 10-year rates of 96% for overall survival (OS), 88% for progression free survival (PFS), and 85% for event free survival (EFS, defined as PFS plus SMN events). RT was spared in 18% of patients and this figure was similar among the 3 treatment groups. Overall, RT-treated patients had superior PFS (10-year rate 92% *vs.* 84% for the no RT group; P=0.004), despite their inferior radiographic response. Although treatment failures were more frequent in non-irradiated patients, OS was almost identical within each TG irrespectively of the use of RT, and, overall, the 10-year OS rate was 99% for non-irradiated *vs.* 97% for irradiated patients (P=0.49).

The results of the GPOH-HD95 trial indicated that RT could be safely omitted in 20% of TG1 patients, i.e., those who achieve a CR according to the criteria of this trial. These patients have a 10-year PFS rate of 97% *vs.* 92% for patients with less satisfactory radiographic response, who were irradiated (P=0.21). The 10-year OS rate was 99% for both groups. These results were confirmed in the subsequent GPOH-HD-2002 trial and cannot be virtually improved in the CR group with the addition of RT (7). However, 80% of these early stage patients are still irradiated. It is tempting to speculate that a CR definition based on Positron Emission Tomography/Computed Tomography (PET/CT) might permit the omission of RT in more patients.

In TG2, RT was spared in 17% of the patients—again those who achieved a CR with chemotherapy—but the 10-year PFS for this group was disappointing: Only 69% remained progression-free versus 91% for patients who were irradiated, despite the less satisfactory radiographic response of the latter. Why non-irradiated CR patients had a so high relapse rate, which was even higher than in TG3? Firstly, TG2 might have included a higher percentage of patients with bulky disease (although disease bulk was not taken into account for risk stratification and was not described in the paper), in whom RT might play a more decisive role. Secondly, the definition of CR permitted the presence of <2 mL residuals. Using the a × b × c × 0.52 formula, for example, a 2.5 cm × 1.5 cm × 1.0 cm residual lesion is still consistent with CR. However, such lesions, or even smaller, may contain viable tumor (demonstrable by functional imaging or not), which will certainly lead to relapse if not irradiated (8). Finally, TG2 patients received a total of 4 chemotherapy cycles, as opposed to 6 for the TG3 group. In spite of the high relapse rate, 10-year OS rates were identical for the 2 groups, reaching 98%! This result highlights the fact that non-irradiated patients in TG2 were easily salvaged. Unfortunately, salvage strategies are not described in the paper.

In TG3, RT was also spared in the 17% of the patients with advanced disease who achieved a CR with chemotherapy: In this group the 10-year PFS was 83% versus 89% for patients who were irradiated, although the radiographic response of the latter was less satisfactory. Despite the 17% 10-year progression rate for non-irradiated patients, the 10-year OS was 100% versus 95% for the irradiated group. The authors concluded that RT

could not be omitted in TG3 even after a radiographic CR. However, RT fields are expected to be more extensive in this subgroup of patients with Ann Arbor stages IIB_E, $IIIA_E$, IIIB ($\pm_E$) or IV. Non-irradiated patients also appear to be easily salvaged even in the setting of advanced disease.

Although GPOH-HD95 points out to the omission of RT in selected patients achieving a CR after chemotherapy, especially those in TG1, more than 80% of the patients are still irradiated. In comparison to the previous DAL-HD90 study (5), RT dose was also decreased for most patients. The major goal would be the identification of those patients with PR/residual masses by imaging, who have no active disease, in order to test the elimination of RT. A negative post-chemotherapy PET might be the selection criterion for a randomized trial assessing this question. Thus, it might be possible to avoid RT in more patients, especially those with advanced stages, who require extensive fields.

Despite the large number of patients included in the GPOH-HD95 trial, its non-randomized design constitutes a major disadvantage. The question whether RT can be omitted in pediatric or young adult patients with HL was examined by the CCG 5942 randomized trial (6,9). Its updated results were reported recently (9). Patients were classified to 3 treatment groups, albeit in a different way compared to GPOH-HD95 trial, taking into account tumor bulk as well. Patients in early and intermediate stages received 4 or 6 COPP/ABV cycles respectively, while advanced stage patients (those with stage IV) received 6 cycles of more intensive chemotherapy containing also high dose cytarabine and etoposide. Patients achieving a CR were randomized either to 21 Gy IF-RT (with even larger than IF-RT fields) or to no further therapy, while all PRs received IF-RT. However, the definition of CR in this trial was less stringent, requiring either complete disease resolution or a >70% reduction in tumor volume in conjunction to reversal of gallium scan from positive to negative. Under this definition, almost 80% of evaluable patients achieved a "CR" and 498 patients were randomized for RT omission or not according to the protocol. The trial was terminated early because of excess relapses in the non-irradiated group. In an "as treated" analysis, the 10-year EFS was 91% versus 83% (P=0.004) for irradiated and non-irradiated patients respectively. In contrast, 10-year OS was almost identical in both groups (97% versus 96%, P=0.50), confirming the salvageability and the overall excellent outcome of pediatric HL. Notably, EFS benefit was evident in early stage patients, but it was not statistically significant in intermediate and advanced stage patients, who had also received more or more intensive chemotherapy.

On the other hand, several trials in adult HL have attempted to assess whether omission of RT is feasible. In early stages without bulky disease or B-symptoms, the addition of RT (alone to the favorable or after ABVD ×2 in the unfavorable group) provides better disease control compared to ABVD ×4-6 alone, but, using rather out-dated, extensive and relatively high-dose RT, 12-year OS appears to be better if RT is omitted (10). Thus, this trial (NCIC HD.6) (10), suggests that better disease control may be even associated with worse OS after sufficiently long follow-up and is increasingly used to support the omission of RT in asymptomatic, non-bulky, limited stage HL, leading to extensive comments and controversies in the literature (11-15). Recent PET-based trials (with interim PET-based design) show that RT may indeed confer smaller or larger benefits in disease control rates even in complete responders to ABVD, as evaluated by PET/CT after 2 or 3 cycles (16,17). However, it is clear that almost 85% of patients will receive unnecessary RT in order to prevent few relapses and an OS benefit is unlikely to be demonstrated (10). In advanced stage disease, a conventional CR after MOPP/ABV (18) or even a good (>75%) PR after MOPP/ABV or ABVPP chemotherapy (19) obviates the need for rather extensive IF-RT or subtotal or total nodal irradiation [(S)TNI] respectively. In fact, non-irradiated patients (who received 2 additional cycles of chemotherapy) might have better OS than the irradiated ones after ABVPP, despite their numerically inferior disease free survival (19). If chemotherapy is more intensive, such as BEACOPP-escalated, RT to residuals >1.5 cm improves PFS by ~6% (although some patients in the no RT arms were actually irradiated) without any effect on OS (20). The current strategy of the GHSG after BEACOPP-escalated is to limit the use of RT to patients with PET-positive residuals measuring >2.5 cm, achieving excellent long-term PFS rates with RT use confined to only 11% of the patients (8).

A secondary target of the GPOH-HD95 trial was to evaluate whether RT-related effects, such as thyroid disorders and SMNs, can be avoided by omitting or reducing RT. The median follow-up of 10 years is still short for the precise evaluation of long-term RT-related SMNs. With 21 observed SMNs, including 17 solid tumors, the 10-year cumulative incidence of SMNs was 3.1% so far. Only 1 SMN developed among the 165 non-irradiated patients, while the remaining were observed in the 735 irradiated patients. Notably, among 17 solid tumors, 14 developed within the RT fields.

What conclusions can be drawn from the GPOH-

HD95 trial? First, RT can be safely omitted in pediatric and adolescent patients with early stage HL achieving a stringently defined CR after 2 cycles of OPPA or OEPA chemotherapy; second, RT could be reduced in case of good PR by conventional imaging, in order to avoid the relatively rare but significant treatment-related late effects, maintaining, simultaneously, the high cure rates; third, conventional response assessment is not the optimal means to decide whether RT is needed or not. Many patients with less than stringent CR may not need RT in the absence of positive post-treatment functional imaging findings (gallium scans). Their selection is expected to be even more effective with the use of PET-scan.

It is now increasingly recognized that RT can be omitted in many patients with HL without compromising the final outcome. One should decide whether a possible increase in early, mainly disease-related mortality, is justified in order to enjoy a decrease in later, side effect-related mortality of higher magnitude. A model-based assessment suggests that the expected mortality after chemotherapy alone becomes lower than that of combined modality approximately 20 years after the initial treatment for a hypothetical 15-year old HL patient (2). However, the net difference in life-years loss between chemotherapy alone and combined modality is very small; in fact it may be <1 year, while the difference in the proportion of patients expected to be alive at age 50 is in the order of 1.5%. Instead of abandoning RT in all patients on the basis of such considerations accepting a considerable proportion of relapses and -probably- some limited degree of early disease-related mortality, it appears wise to try to stringently limit RT in those patients who really need it, through the use of modern functional imaging. Such efforts are already in progress and results regarding efficacy are awaited relatively soon (21).

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Footnote

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