

# Pediatric Hodgkin Lymphoma: on the road to a 'radiotherapy-free' cure rate? – Commentary on a report on final results of the Multinational Trial GPOH-HD95

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During the last four decades, the treatment of children and adolescents affected by classic Hodgkin Lymphoma (HL) has achieved continuous and dramatic improvements in response and survival rates, from uniform fatality up to curability for 90% of patients (1). This success has occurred mainly in economically advantaged countries due to constant participation of children in clinical trials, the administration of pediatric cancer care in specialized centers and the continuous efforts in refining treatment intensities against the gradually discovered profiles of subacute and delayed complications of radiotherapy (RT) and multiagent chemotherapy (2,3). As a matter of fact, due to active growth and development at the time of treatment, youngsters and children may suffer of impaired growth of soft tissue and bones, and have a greater sensitivity as compared to adults, in developing thyroid and gonadal dysfunction, cardiopulmonary toxicity, and secondary neoplasms (4). In a large series including 1,876 pediatric HL survivors, the estimated cumulative incidence rates of total (grade 1 to 5) and severe grade (grade 3 to 5) chronic medical conditions were 75% and 40%, respectively, at 25 years follow-up (5).

As a result of these findings, treatment protocols have evolved over time to maximize tumor control while minimizing late iatrogenesis: the exposure to anthracyclines has been reduced, the cumulative dosage threshold of bleomycin and alkylating agents progressively lowered, the use of RT limited from treatment schemes (6,7). So, despite childhood HL is one of the few pediatric tumors that shares biological features and natural history with an adult cancer, treatment paradigm employed by pediatric oncologists have largely diverged

from that adopted when devising treatments for adults with HL. As these latter have focused primarily on treatment intensification, dose escalation and extensive use of RT, contemporary programs for pediatric HL have adopted a risk-adapted approach in which patients receive the most effective chemotherapeutic agents at lowered doses of each component, for a limited amount of cycles, in short durations, in conjunction with low-doses of radiation delivered in small volumes (3). This strategy is the last step in a long journey of tuning up the risk-benefit ratio for each antineoplastic agent and treatment, which has resembled the raise of a delicate fairytale brick castle with small pieces rightly suited and juxtaposed through prudent additions and removals. More recently, even the exclusion of RT has been suggested.

In this regard, relevant insights come from the Journal of Clinical Oncology, where Dorff *et al.* (8) report results of the large multinational HD95 trial, coordinated by the German Society of Pediatric Oncology and Hematology (GPOH). This study investigated a response-adapted treatment strategy where patients in CR after chemotherapy did not receive consolidation RT, and those in good partial remission (i.e., >75% tumor volume reduction) had a reduction in the standard radiation dose from 25 to 20 Gy through a reduced involved-field RT. The trial enrolled 925 pediatric HL patients, allocated to three treatment groups based on early-, intermediate-, and advanced-stage disease. Overall 165 patients (18%) did not receive consolidation RT upon achieving CR. The omission of RT was safe for complete responders with early stage but detrimental in intermediate and advanced stage. For early-

stage patients who received (n=262) or did not receive (n=66) RT, progression-free survival (PFS) at 10 years was 92.2% and 97.0%, respectively, and overall survival (OS) 98.2% and 98.5%. Differently, in the group of intermediate stage disease, patients not receiving RT (n=43) had far worse PFS as compared to those irradiated (n=211) (68.5% *vs.* 91.4%,  $P < 0.001$ ). This latter trend was also observed in patients with advanced-stage disease, although did not reach statistical significance. As to patients with more than 75% tumor volume regression, a direct comparison was performed Dorff *et al.* (8) between HD95 using 20 Gy as consolidation RT and the previous DAL-HD90 study from the same cooperative group, adopting 25 Gy irradiation. Due to superimposable results observed in PFS, 95% and 94%, respectively, the Authors concluded, with the caveat of historical comparison in a nonrandomized fashion, that standard radiation dose could be reduced from 25 to 20 Gy. Finally, the Authors, on the basis of results from registered late adverse events, pointed out that the omission of RT may reduce the frequency of hypothyroidism and avoid thyroid secondary cancer.

Studies from GPOH have a continuous tradition, from 1978, of progressive introduction of changes of treatment policy aimed at improving the trade-off between disease control and iatrogenesis. This GPOH-HD95 trial had the merits of demonstrating that a chemotherapy response-guided RT strategy in children and adolescents is feasible (<2% protocol violations), and the omission of consolidation RT can be safe in individuals with early-stage disease after achieving a CR following few cycles of induction chemotherapy. Also relevant is evidence that irradiation dose for incomplete responders can be reduced from 25 to 20 Gy without affecting failure rate. These results have been recently confirmed and supported, albeit at a shorter follow-up time, by the GPOH-HD-2002 study (9), and seem to open the way for an overall reduction in the presence of RT in the treatment of pediatric HL.

Anyway, some caution should be exercised when extending the conclusions of GPOH-HD95 trial to a general clinical practice setting or to a worldwide application. Results reported by Dorff *et al.* have been obtained in a trial with a specific definition of risk group, a strict definition of anatomical response and a central evaluation of all imaging results, before and during treatment. Definitions of ranks of risk and response vary among countries and study groups while disease staging and RT modalities may differ from center to center, due to hospital factors and access to technical innovations in radiation equipment. The

assistance and close control from a coordination center and a centralized review are not commonly available, and results may not be reproducible outside such qualified setting. In addition, the results achieved in the GPOH-HD95 trial may be strictly related to the chemotherapy regimens OPPA (vincristine, procarbazine, prednisone, and doxorubicin) and OEPA (vincristine, etoposide, prednisone, and doxorubicin) delivered in the trial, and may not fit in with other protocols based on alkylating agents or derived from the seminal regimen ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) (10). So, for instance, a statistically significant increase in treatment failure was found in the CCG 5942 randomized trial from Children's Cancer Group (11) when RT was omitted in patients with 'favorable' early stage who were complete responders to COPP/ABV regimen. In addition, trends on the application of consolidation RT in the last decade show that 46% to 67% of adult patients treated with ABVD still require irradiation to maintain adequate PFS (12,13) while use of RT has been progressively reduced in the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) platform from 71% (HD9) to 38% (HD12) down to 11% (HD15) without worsening survival (14).

The substantiation by Dorff *et al.* (8) that the standard dose of consolidation RT for incomplete responders can be safely reduced to 20 Gy may not ultimately lessen post-actinic sequelae. Some evidence exists that reduction in radiation dosages and size of irradiation fields may not abrogate the risk for RT-related sequelae in survivors of pediatric HL (15). Also, the number of deaths due to cardiovascular and second cancers in the German HD10 trial using 20 Gy already exceeds those caused by HL at 7.5 years of follow-up, suggesting that the use of lower doses and smaller volumes may not have sufficient effect to avoid radiotherapy complications, which contribute to excess longer-term mortality (16). Indeed, belated-effects mortality details on survivors treated more recently will not be attainable for many years, and clinical trials comparing the outcome of combined chemotherapy and radiotherapy *vs.* chemotherapy alone cannot feasibly capture all risks associated with late effects. Decision-analytic approaches have been described, both in pediatric (17) and adult (18) setting, which can provide informative tools for exploring the trade-offs between short- and long-term risks of death by leveraging the best available clinical data now.

A strategy both 'risk-based' and 'response oriented' such as that adopted in the GPOH-HD95 trial could be now enhanced through the incorporation of

18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET), both at staging and response assessment. In the treatment strategies devised for HL in adult patients, an early response at 18F-FDG PET functional imaging retains prognostic value and is currently under evaluation to titrate therapy so to minimize treatment intensity in case of rapid early response and thereby reduce toxicity, while intensifying treatment for those with slow early response, thereby improving disease control (19). However, as pathogenesis, histology and tumor environment composition of HL in children and adolescents may differ from adult HL patients, the incorporation of 18F-FDG PET in pediatric protocol and its positive and negative predictive values should be carefully evaluated (20).

The road toward a RT-free chemotherapy would be especially good news for countries in the world where access to radiotherapy technologies may be limited and innovation in radiation equipment problematic. It is not surprising that the omission of RT had been tested before in non-European countries (21-24). However, the stages should not be forced. Curtailing a little on the radiation dose and cutting back a little on the chemotherapy cycles, has demonstrated thus far to preserve the antitumor effects and minimize the toxicity of a combined modality therapy. Recent evidences supporting restriction of RT volumes through the adoption of involved node RT, i.e. irradiation limited to the specific lymph nodes initially involved with disease, suggest further caution in dismissing RT (25). The point that OS may persist uncompromised in case of disease recurrence (due to excellent response to salvage therapy) should not lead to relent, since treatment for relapse generally relies on high dose therapy followed by autologous stem cell transplantation and predisposes individuals to additional morbidity and excess risk of mortality.

The balance achieved between cure and iatrogenic events is fragile as the steadiness of the high magical brick castle named 'cure rate' which has been raised patiently through decades for children and adolescents affected by HL. Additions and removals of brick pieces should be repeatedly experienced and carefully validated.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to

declare.

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