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Supplement Article

XVII. Radiotherapy in early stage Hodgkin lymphoma

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The treatment of patients with Hodgkin lymphoma (HL) is one of the major success stories in oncology and 60–90% of patients are cured of their malignancy depending on clinical stage and risk factors. Radiotherapy was used to cure patients with HL as early as the 1940s, but more widespread successes came in the 1960s for early stage diseases I A and II A with the use of extended field radiotherapy (RT) techniques to include all nodal stations above the diaphragm such as the 'mantle' field [1]. Recurrence of disease outside the radiation field in some patients led to studies of adjuvant chemotherapy as part of a combined modality approach. These studies led to improved progression free survival (PFS) but no overall survival (OS) advantage was seen over RT alone because patients developing recurrent disease after RT were very efficiently salvaged by chemotherapy [2].

A sequential and thorough approach in large randomized trials exemplified by the German Hodgkin Study Group (GHSG) has led to substantial treatment reduction and established a standard of care based on minimal highly effective combined modality treatment (CMT). With a median follow-up of 7.5 years, 8-year results of the GHSG HD10 trial involving 1370 patients with early stage favourable HL showed that two cycles of chemotherapy regimen consisting of Adriamycin, Cyclophosphamide, Oncovin, Procarbazine, Prednisolone (ABVD) and 20Gy of involved field radiotherapy (IFRT) were as effective as four cycles ABVD and 30 Gy, produced less immediate toxicity and resulted in an OS of 95% and freedom from treatment failure and event-free survival of 86% [3]. For early stage unfavourable HL, moderate dose escalation using a chemotherapy regimen consisting of Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin, Procarbazine and Prednisone (BEACOPP) did not significantly improve outcome over four cycles of ABVD and 30 Gy IFRT, which the GHSG HD11 concluded remains the standard of care [4] Whilst efforts to improve a 5-year Failure From Treatment Failure (FFTF) of 85% and OS of 94.5% are ongoing in unfavourable disease, it will be difficult to improve the results of two cycles of ABVD and 20 Gy for the favourable group. Given that improvements in these excellent results with CMT are unlikely to happen, there have understandably, been a focus on maintaining high cure rates but decreasing acute and late toxicity of treatment. The late toxicity of treatment is clearly important given the young age of most patients and the excellent outlook after treatment with prolonged survival of decades expected for the majority. Much of this focus of treatment-induced late effects has been on RT as this data is the most mature and well-studied. The severe late effects of RT have been increasingly recognized in the last 20 years and include secondary malignancies, thyroid abnormalities and cardiovascular disease [5] These side effects correlate with large radiation field sizes and doses that are no longer used in modern practice and which precipitated the substantial reduction in the size of the radiation fields and doses. Although subtotal nodal or extended field techniques were used historically, this changed to involved field and more recently involved node and involved site that reduces the nonspecific irradiation of healthy tissue by up to 10-fold.

The current scientific discussion is centred on finding the right balance between toxicity and cure of HL. The role of RT that plays in achieving this goal of cure has become highly controversial and at times discussion is coloured by bias and opinions of the modality of the treatment specialist. The controversy of the use of RT essentially distills down perhaps two important questions

(1) Do the long term risks of radiotherapy when used as part of combined modality therapy abrogate the initial gain in local control and PFS such that chemotherapy alone may be the better long term option?
(2) Does the application of modern RT approaches using involved site techniques leading to the substantial reduction in field size and reduced RT doses off set the late toxicities associated with extended fields and higher RT doses leading to improved long term survival?

Recent discussions about the role of RT versus chemotherapy alone in early HL were further stimulated by the

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clinical trial published by Meyer and colleagues [6]. In this trial (HD.6) conducted by the National Cancer Institute of Canada Clinical Trials Group, 405 previously untreated stage I A or II A non-bulky HL patients were randomly assigned to chemotherapy (ABVD) alone or a large-field radiotherapy-containing treatment strategy. In the group that was assigned to radiation, a favourable cohort of 64 patients received subtotal nodal irradiation (STNI) only, and the unfavourable cohort of 125 patients was treated with two cycles of ABVD followed by STNI. Those assigned to ABVD who responded to treatment received four cycles of the chemotherapy, and those with less than a complete remission had a total of six cycles of ABVD. The HD.6 study was closed prematurely in April 2002, soon after results emerged from the EORTC H8-F trial reporting excellent outcomes with CMT that included the significantly smaller involved field radiation therapy. The trial committee felt that continuing with a protocol that included STNI would therefore be inappropriate. The initial report of this trial at a median follow-up of 4.2 years reported no difference in OS. However, now, with longer follow-up, OS was superior in the ABVD alone arm of the trial where there were 12 deaths compared with 20 deaths in the STNI arm (94% versus 87%, $p = 0.04$). Crucially, deaths in the ABVD arm included six from HL or early treatment toxicity and six from other causes (four second cancers and two cardiac). In the STNI arm, there were four deaths from HL or early treatment toxicity and 20 from other causes (10 second cancers, two cardiac, three infective and five other). Freedom from disease progression was 87% in the ABVD alone group and 92% in the STNI group ($p = 0.05$) and the authors concluded that OS was better in the chemotherapy alone group because of a higher incidence of deaths from other cases in those receiving STNI.

Many of the excess deaths in the STNI arm of this trial may be attributed to late treatment toxicity; however, further clarification of whether the second cancers lie within the radiation field is unclear in the publication and this data are still awaited. Perhaps of greatest concern in the interpretation of these results are the five deaths categorized as 'other' may or may not have been treatment related. Although the inclusions of suicide, Alzheimer's disease, accidental drowning and death of unknown cause into the survival estimation is correct from a statistical point of view, these deaths appear rather misleading from a medical point of view and are obviously not attributable to radiotherapy. No death of 'other' causes has been documented in the chemotherapy alone group. This imbalance is highly misleading in favour of the chemotherapy alone group. Without these deaths of 'other' causes, there would have been only 19 events in the RT group and there is no longer significance for OS. This imbalance is due to an undersized and incompletely recruited study with a small number of events. Without these unusual events, this would have been a negative study without a survival difference (primary objective) but with a significantly better tumour control for the RT group. Perhaps not surprisingly, this trial has also attracted a number of criticisms and comments within the clinical community, including objections to the outdated large-field radiotherapy used and the statistics reported. The results do however underline the fact that improving long-term survival in early stage HL is not only dependent on reducing the number of deaths from progressive disease but also on developing treatments with less late toxicity. Although late effects are clearly important, the biggest risk in this interpretation of this study is to focus so much on reducing late toxicity of RT that we compromise the delivery of curative treatment using established effective combined modality approaches; where it is self-evident that long-term survival requires effective initial therapy. There is now compelling evidence, to address the second question posed earlier regarding the application of modern RT techniques. Long-term complications appear to be much reduced, as would be expected by employing considerably smaller radiation field sizes that decrease the volume of tissue by up to 10-fold [7]. Although the NCIC/ECOG trial demonstrates that four to six cycles of ABVD alone is an effective treatment for many patients with stages I A and II A, an important question not addressed by the trial is—'What are the acute and late consequences of replacing abbreviated chemotherapy and modern small RT field with no RT and more cycles of chemotherapy? A recently published analysis of older patients recruited onto the GHSG H10 and H11 studies outline the poor tolerance and reduced dose intensity of chemotherapy achieved in older patients [8]. For ABVD, the doxorubicin is predicted to produce an excess of cardiovascular mortality along with an under reported but alarmingly high incidence of Bleomycin lung injury and lung function impairment in routine clinical practice [9]. In one study, nearly 30% of the patients were found to have dyspnoea on exertion and associated reductions in pulmonary function tests. In the multivariate analysis, chemotherapy with bleomycin–anthracyclines was the only significant predictor for lung function impairment [9]. The cardiotoxicity of doxorubicin is dependent on cumulative dose [10] and a patient receiving six cycles of ABVD will be exposed to a total dose of 300 mg/m^2, where there is clear evidence of increased cardiac mortality with a peak incidence of 15–19 years after treatment and the increased risk may persist for 25 years [11]. In addition, recent randomised trials should perhaps also send a note of caution to those advocating chemotherapy-only approaches. In the EORTC-GELA H9 trial for early favourable HL, the failure-free survival at 5 years was significantly reduced in patients who did not receive additional radiotherapy after six cycles of chemotherapy (epirubicin, bleomycin, vinblastine, prednisone). When chemotherapy was compared with CMT, the meta-analyses found significant differences in

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terms of tumour control and OS favouring combined modalities in early stage HL patients. [12].

There is currently intense interest on a risk-adapted approach to therapy using fluorodeoxyglucose (^{18}F) positron emission tomography (FDG PET) as an imaging biomarker to determine the subsequent treatment based on an assessment of response after initial cycles of chemotherapy. In the UK National Cancer Research Institute RAPID trial, 602 patients were registered (2003–2010) with non-bulky stages I A and II A HL who received three cycles of ABVD followed by a PET scan. If this scan was 'positive' at central review, a fourth cycle of ABVD and IFRT were given. Those with a 'negative' PET scan on the other hand were randomised between no further treatment and IFRT. The results were presented at the American Society of Hematolgy's annual meeting in 2012, after a median follow-up of 48.6 months [13]. In this study, interestingly after three cycles of ABVD, only 74.7% patients were deemed PET negative. The intention to treat analysis in 420 PET negative patients demonstrated a 3-year PFS of 94.5% in the IFRT arm and 90.8% for no further treatment (HR 1.51, $p = 0.23$). Importantly, however, 25 of 209 patients randomised to IFRT did not receive this treatment. If a per protocol analysis of the 392 PET negative patients was performed, the 3-year PFS demonstrated a highly significant advantage in favour of RT with an excellent PFS of 97.0% for IFRT and 90.7% for no further treatment (HR 2.39, $p = 0.03$). The survival analysis in this study is also worthy of comment with five of the six deaths in the IFRT arm occurring before the patients actually received RT in older patients (over 60 years) from causes related to the preceding chemotherapy, with again the toxicity and poorer tolerance of chemotherapy as highlighted earlier with the HD10 and HD11 studies [9]. The early treatment toxicity with chemotherapy for HL is perhaps too readily considered as minor and having little impact on survival. The UK NCRI study highlights two recurrent potential problems, namely, acute toxicity may be a greater challenge for older patients than late toxicities, and smaller studies with fewer events can lead to a disproportionate number of random events such as those occurring in the 'radiotherapy arm', which have no relationship to the RT. Crucially in the interpretation and application of the RAPID trial results, the data has been obtained in the setting of a quality controlled PET image acquisition with central review of PET images at a core laboratory using a conservative definition of what represents PET negative. All of which are not yet reproducible in routine practice. Finally, given the lessons from recent trials, longer follow-up is required to establish the impact of a PET directed approach on 10-year and 20-year survival and cause of death to be confident that this approach is safe and effective. The EORTC-GELA-IIL H10 study in patients with early favourable and unfavourable disease also provides additional relevant data as regards risk adjusted therapy. In this PET-guided trial, the chemotherapy-only arms in patients who were PET negative after two cycles of ABVD had to be closed due to significantly more events, in both the early favourable (one in INRT versus nine in no further treatment) and early unfavourable (seven INRT versus 16 experimental arm). The Independent Data Monitoring committee has concluded that based on the results, it is ***unlikely*** that the primary objective of the trial will be met; which holds for both favourable and unfavourable groups [14].

Conclusions

Second cancers and cardiovascular disease are increasingly recognized to erode long-term survival in early stage HL where the primary disease was eliminated years earlier. In this respect both radiotherapy and chemotherapy are implicated and our focus as oncologists should be on designing therapies capable of maximizing cure and minimizing late toxicity and testing these in clinical trials that address the relevant endpoints; OS and cause of death [15,16].

The major problem in the controversy of combined modality versus chemotherapy-only strategies in early stage HL is the lack of randomized trials comparing chemotherapy alone versus CMT. Few trials have used identical numbers of chemotherapy cycles that would allow for a proof of principle of chemotherapy alone concepts [17].

The GELA H9 and EORTC-GELA H10 data argue strongly against the use of chemotherapy alone in early stage HL outside of clinical trials, as does the meta-analysis [12]. In order to change the current standard approach of CMT in early stage HL, sufficiently powered prospectively randomized trials of high quality are needed. Therefore, the GHSG HD10 trial approach of two cycles of ABVD followed by 20 Gy of IFRT appears to retain its position as a highly effective, well-tolerated standard of care for patients with stages I A/II A, favourable, classical HL, where the toxicity could be further decreased with reduction in RT field size from IFRT to involved site RT (ISRT).

Are we ready to move to response-adapted treatment approaches potentially using FDG PET imaging to select patients who may have an excellent outcome with abbreviated chemotherapy alone? Although this approach appears promising, ongoing challenges remain regarding the routine interpretation of PET CT scans in clinical practice that suggest any such move to risk adjusted approaches may be a little premature. All of the emerging clinical trials using FDG PET continue to highlight the superiority of combined modality therapy over chemotherapy alone and also the difficulties associated with interpretation of PET 'negative' even amongst expert panels. There are simply too many well performed large randomised studies today demonstrating that abbreviated chemotherapy followed by small-field radiotherapy is the best available choice of treatment for patients. Therefore, the evidence at the

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current time would suggest that outside of clinical trial, the majority of patients with early stage HL are most safely treated with CMT.

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