Review

Radiotherapy in early stage Hodgkin's disease: Principles and results of recent clinical trials

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Summary

For decades, radiotherapy has been used as a single treatment modality for early stage Hodgkin's disease. In recent years, late radiation effects, such as myocardial infarctions and induced solid tumours, have become of major concern. It now seems clear that chemotherapy coupled with radiotherapy not only improves relapse-free survival, but can also replace radiotherapy as adjuvant treatment for subclinical disease. This offers the opportunity of reduction of extended fields and high doses, which hopefully correlates with lower late radiation toxicity. The challenge for clinical trials on the treatment of early stages Hodgkin's disease in the coming years will be the trade-off between adjuvant radiotherapy and adjuvant chemotherapy, reducing radiotherapy in volume and dose without jeopardising the 90% overall survival that can be achieved nowadays.

Key words: chemotherapy, combined modality treatment, early stages, Hodgkin's disease, induced tumours, late toxicity, radiotherapy

Introduction

In the treatment of early stage Hodgkin's disease (HD), radiotherapy can have two different applications. First, it can be used as a single modality treatment, classically in extended fields such as mantle field (MF), subtotal nodal irradiation (STNI) or total nodal irradiation (TNI). Second, it can be part of a combined modality treatment (CMT), used for consolidation during or after chemotherapy. Here, the irradiation can be given on extended fields again, but it is usually limited to previously involved areas (IF), to areas with bulky or slowly regressing disease (so called 'iceberg' irradiation) or to areas with residual masses.

A clear dose-response relationship has been established. For macroscopic or residual disease, a dose of 36–40 Gy is necessary for local control. In previously involved areas, which are in complete remission (CR) after chemotherapy, a dose of 30 Gy is sufficient. For uninvolved, electively treated areas, a dose of 20–24 Gy may suffice.

Toxic side-effects from the irradiation can be acute, subacute or late. Acute toxicity comprises erythema, oesophagitis and hair loss. Subacute effects are pneumonitis, pericarditis, Lhermitte's sign and subcutaneous fibrosis. Late effects are hypothyroidism, coronary stenosis and induced malignant tumours. Solid tumours in particular are thought to be caused by irradiation, for example lung cancer, breast cancer, gastrointestinal malignancies, and skin cancer [1].

Because chemotherapy has different side effects, such as bone marrow depression, sterility and other types of induced malignancies (leukaemia, non-Hodgkin's lymphoma), the combination of chemotherapy and radiotherapy in CMT could produce fewer or less serious side effects.

In the past 10 years, several clinical trials on early stage Hodgkin's disease made radiotherapy subject of their investigation. These trials generally tried to make the fields smaller or the dose lower, with the purpose of reducing long term radiation toxicity, keeping relapse-free survival and overall survival constant.

Clinical trials with a radiotherapy question

No radiotherapy in the experimental arm

Four randomized studies have compared an arm with radiotherapy to an arm without radiotherapy. The first two studies, from the NCI USA [2] and from Italy [3], produced conflicting results: in both studies, pathologically staged patients were treated with either extended field radiotherapy or six courses of MOPP. In the American trial, disease-free survival (DFS) and overall survival (OS) were not significantly different. In the Italian trial, there was no difference in DFS, but a large difference in OS (93% vs. 56%) in favour of the radiotherapy. The explanation of Biti (poor salvage possibilities in the MOPP-arm) has been criticised by Longo [4].

In the third, still ongoing study of the NCI Canada, one of the arms with extended field irradiation is being
compared to one of the other arms using four to six courses of ABVD without radiotherapy [5].

In the fourth study, from the GATLA in Argentina [6], chemotherapy only (six courses of CVPP) was compared with CMT (six courses of CVPP, sandwiched with IF radiotherapy). In favourable patients, DFS and OS were similar, but in unfavourable patients CMT was significantly better than chemotherapy alone (DFS: 75% vs. 34%, OS: 84% vs. 66%).

Radiotherapy volumes smaller in the experimental arm

At the moment, at least six ongoing studies are comparing STNI with IF irradiation. In four trials, STNI alone is compared to chemotherapy combined with 30–36 Gy IF irradiation. The chemotherapy treatments consist of: six courses of EBVP (EORTC, H7-F trial [7]), six courses of VBM (Stanford, Gl trial), three courses of ABVD (SWOG) and three courses of MOPP/ABV hybrid (EORTC, H8-F trial).

Two trials are comparing chemotherapy plus STNI to chemotherapy plus IF. The chemotherapy treatments consist of: four courses of MOPP/ABV hybrid in the EORTC H8-U trial and 2COPP/2ABVD in the GHSG HD-8 trial.

Finally, in the BNLI, mantle field irradiation is being compared to VAPEC-B chemotherapy plus IF irradiation.

Smaller radiotherapy volume as standard treatment

Some groups have decided to reduce their extended field radiotherapy to mantle field irradiation alone, taking into account (very) favourable prognostic factors such as clinical stage I (female, mediastinum), lymphocytic predominance histology or high cervical presentation. Among those groups are the Stanford group [8], the Harvard group [9], the Toronto group [10], and the EORTC (H7-VF and H8-VF trials) [7]. In the prospective non-randomized H7-VF study, overall survival of the 40 patients was excellent (six-year OS 97%), but event-free survival was disappointing low (six-year EFS 68%) [11], which even led to discontinuation of the H8-VF study.

Dose reduction

The German Hodgkin Study Group in particular has studied the question of dose–response relationship and dose reduction. In the HD-4 trial, extended field radiotherapy of 40 Gy was compared to extended field radiotherapy of 30 Gy, followed by involved field radiotherapy of 10 Gy. It was concluded, that subclinical disease could sufficiently be treated with 30 Gy [12]. The HD-1 trial of the GHSG tested the value of 40 Gy vs. 20 Gy on areas with possible subclinical involvement after treatment with 2COPP/2ABVD courses. The results suggested no relevant radiotherapy dose effect in the range between 20 and 40 Gy in non-bulky involved as well as in uninvolved areas [13]. The coming EORTC H9-F trial will test three dose levels on involved fields after CR with six EBVP courses: 36 Gy, 20 Gy and 0 Gy.

Conclusions from studies on radiotherapy in early stage Hodgkin’s disease

The main issue in all studies is the balance between an excellent overall survival (> 90%) and the late radiation toxicity, especially cardiac disease and induced solid tumours.

It seems that radiotherapy as a single treatment modality can be safely replaced by a combination of chemotherapy and less radiotherapy, without jeopardising the good overall survival. Meta-analyses by Shore [14] and Specht [15] show that combined modality treatment does not produce better overall survival, but improves relapse-free survival.

Using chemotherapy in early stage Hodgkin’s disease, the extent and possibly the dose of radiotherapy can be reduced, hopefully resulting in less late toxicity in the future.

References

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