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ORIGINAL ARTICLE

Radiotherapy for Hodgkin's lymphoma: too hard to die?

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Summary

The treatment of Hodgkin's lymphoma (HL) is associated with significant toxicity. The objective of high quality management is to keep the concept of combined modality, while trying to decrease the radiation dose, to diminish to a great extent the irradiated volume and at the same time to reduce the number of chemotherapy courses, introducing the so-called optimisation. New directives should be followed to obtain more effective treatments of HL. Shorter cycles of chemotherapy and the utilization of modern techniques in radiotherapy (RT) constitute fundamental steps to achieve this objective. Analysis of randomized studies supports the inclusion of reduced-field and dose of RT in the radiotherapeutic treatment options for HL. RT is an integral part of the combined-modality therapy (CMT) of HL.

Key words: chemotherapy, Hodgkin's lymphoma, new agents, radiotherapy

Introduction

HL has become one of the most curable malignancies nowadays. It affects young people and requires meticulous assessment, choice of proper treatment(s) and response evaluation to maximize cure and minimize treatment-related toxicities. Patients with early and advanced stages can be cured with modern RT techniques without morbidities. Several studies have attempted to reduce long-term treatment-related side effects, such as secondary malignancies and cardiac toxicity, by reducing the cycles of chemotherapy using CMT [1-5].

Methods

The aim of this review was not only to re-examine the historical and the current role of RT in HL, given the latest evidence of an increasing role of RT for the treatment of this malignancy, but also to discuss the available data in relation to treatments and outcomes to date and to propose how future studies and evaluations might be constructed for this disease. A literature search was performed through PubMed Plus, using the following keywords: Hodgkin's lymphoma, radiotherapy, chemotherapy, new agents. Original articles, reviews and commentaries on HL were registered and analysed.

Results

Randomized studies of treatment for early-stage HL

Studies have evaluated the optimal regimen, which consists of not only a number of cycles of chemotherapy and the optimal RT dose and field size as part of CMT, but also the elimination of RT. CMT represents the current standard of care for most patients with early-stage HL [6-10]. Detailed and summarised trials are shown in Table 1.

In the European Organization for Research and Treatment of Cancer (EORTC) H9F trial, patients who were treated with 6 cycles of EBVP (epirubicin, bleomycin, vinblastine, and prednisone) and the ones who had a complete response (CR) were randomized to 1 of 3 groups: no RT; 20 Gy with involved-field RT (IFRT); or 36 Gy IFRT. The no-RT group was closed early. At

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Table 1. Randomized studies in early-stage HL comparing combined-modality therapy with chemotherapy alone

Studies	*Stage*	*Treatment arms*	*OS*	*p-value*
EORTC/GELA H9F (489 pts) [6]	I-II favorable	EBVP×6 vs. EBVP×6+IFRT 20 Gy vs. EBVP×6+IFRT 36 Gy	4 yr	0.001
Tata Memorial Hospital (179 pts) [7]	I-IV (I-II 55%)	ABVD×6 vs. ABVD×6 + IFRT 30 Gy	8 yr	0.01
Memorial Sloan Kettering Cancer Center (152 pts) [8]	I-III A/B, non bulky	ABVD×6 vs. ABVD×6 +EFRT/IFRT	5 yr	NS
National Cancer Institute of Canada HD6 (276 pts) [9]	I-II unfavorable, non B, or bulky	ABVD×4-6 vs. ABVD×2 + STLI	5 yr	0.004
Children's Cancer Group 5942 (501 pts) [10]	I-IV (I-II 68%)	COPP/ABV×4-6 vs. Same + IFRT 21 Gy	3 yr	0.02

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine, ABV: doxorubicin, bleomycin, vinblastine, IFRT: involved-field radiotherapy, EFRT: extended-field radiotherapy, STLI: subtotal lymphoid irradiation, EBVP: epirubicin, bleomycin, vinblastine, prednisone, COPP: cyclophosphamide, vincristine, procarbazine, prednisone, pts: patients, OS: overall survival, yr: year, NS: nonsignificant

the completion of the study, there was no difference between adding consolidation RT of 36 Gy or 20 Gy, but there was a significantly lower failure-free survival in 4 years if no-RT was added (failure-free survival 87, 84 and 69%, respectively; p = 0.001). In 4-year median follow-up no survival difference was detected among the groups that received 20 and 36 Gy IFRT [6].

Researchers at Tata Memorial Hospital in India [7] conducted a randomized trial in which 179 patients who achieved CR after 6 cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) were randomized to receive either consolidation IFRT or no RT. Among the randomized patients, 55% had stage I or II HL, 46% were aged <15 years and 69% had mixed-cellularity histology. Patients in the RT arm had significantly higher overall survival (OS) than the ones in the no-RT arm (8-year OS, 100 vs. 89%; p = 0.002). Patients in the RT arm also had a significantly higher rate of event-free survival (8-year rate, 88 vs. 76%; p = 0.01). The results of this study may not necessarily be pertinent for all early-stage HL patients, for the pediatric ones in stages III or IV and for the mixed-cellularity cases.

In a randomized trial at the Memorial Sloan-Kettering Cancer Center [8], 152 patients with stage IA-IIIA nonbulky HL were treated with either 6 cycles of ABVD or 6 cycles of ABVD –and being in CR or partial response (PR)– followed by consolidation RT (IFRT in 14%, modified extended field in the rest). At 5 years CR duration and freedom from progression for ABVD plus RT vs. ABVD alone was 91 vs. 87% (p = 0.61) and 86 vs. 81% (p = 0.61), respectively. OS was 97% with ABVD plus RT vs. 90% with ABVD alone (p = 0.08). However, this trial closed early because it was not powered to detect any differences among the treatment groups.

The National Cancer Institute of Canada Clinical Trials Group/Eastern Cooperative Oncology Group trial HD-6 [9] randomized patients with clinical stage I-IIA non-bulky, supradiaphragmatic HL to ABVD alone or to ABVD plus RT. The patients randomized to chemotherapy plus RT received subtotal nodal irradiation if considered as favorable risk or CMT (2 cycles of ABVD followed by subtotal nodal RT) if considered as unfavorable risk. The patients were randomized to chemotherapy alone received 4-6 cycles of ABVD using a response-adapted strategy. At a median follow-up of only 4.2 years there was a modest but statistically significant difference in 5-year freedom from disease progression favoring the strategy that included RT (93 vs. 87%; p = 0.006), but the OS was similar between the study groups. Thus, chemotherapy alone (ABVD) may be a sound treatment option for patients with early-stage favorable HL. However, longer follow-up is required to rule out potential pulmonary and cardiac late toxicities associated with ABVD or possible treatment-related second malignancies associated with the use of subtotal nodal irradiation. Originally, this study was statistically designed for a 12-year analysis of survival.

In the Children's Cancer Group (CCG 5942) trial [10], 501 patients aged <21 years who achieved CR with combination chemotherapy (mostly COPP/ABV4 for 6 cycles), were randomized to receive either low-dose IFRT (21 Gy) or no RT. Of the randomized pa-

tients, 72% had stage I or II HL. The 3-year event-free survival with an intent-to-treat analysis was 92% for patients randomized to receive RT and 87% for those randomized to no RT (p= 0.057).

Moreover, a meta-analysis was realized by the Cochrane Haematological Malignancies Group [11], to compare the CMT in early-stage HL with chemotherapy alone. Five randomized controlled trials involving 1245 patients were included. Despite the fact that the CR rate was similar in both categories, tumor control and OS were significantly better in patients receiving CMT. The hazard ratio was 0.40 (95% CI 0.25-0.66) for tumor control and 0.41 (95% CI 0.27-0.60) for OS.

The German Hodgkin's Study Group (GHSG) HD10 trial [12] investigated whether the number of ABVD cycles and the total dose of IFRT may be safely reduced for early-stage favorable HL. Patients with disease stages I and II, without risk factors, were randomized to CMT including 2 or 4 cycles of ABVD followed by a total dose of 30 Gy or 20 Gy of IFRT. After a median follow-up of 85 months, there was no significant difference between ABVD × 4 and ABVD × 2 in terms of 5-year OS (OS: ABVD × 4: 97.1%; ABVD ×2: 96.6%), freedom from treatment failure (FFTF: 93.0 vs. 91.1%) and progression free survival (PFS: 93.5 vs. 91.2%). As for RT, there were also no significant differences between patients receiving 30 Gy IFRT and those with 20 Gy IFRT in terms of OS (97.6 vs. 97.5%), FFTF (93.4 vs. 92.9%) and PFS (93.7 vs. 93.2), respectively. Also no significant difference was detected in terms of OS, FFTF and PFS when all 4 groups were compared.

Randomized patients with clinical stage IA or IIA of HL were studied in the Southwest Oncology Group/ Cancer and Leukaemia Group B trial [13]. This study compared the subtotal nodal irradiation with the CMT, which consisted of 3 cycles of doxorubicin and vinblastine followed by RT. The closure of this study was due to a significantly better failure-free survival rate in the CMT group compared with subtotal nodal irradiation. OS was not significantly different between the two study groups. The CMT was found to be safer in terms of toxicity and development of second malignancies than the subtotal nodal irradiation alone.

The German Hodgkin's Lymphoma Study Group (GHSG) HD7 trial [14] randomized patients with clinical stage IA-IIB favorable HL to either extended-field RT or 2 cycles of ABVD followed by the same RT protocol. There was a significant difference in the 7-year FFTF rate, favoring the CMT arm, but the 7-year OS was similar between the study arms. This study concluded that 2 cycles of ABVD followed by extended-field RT is more effective than the extended-field RT alone.

Bonadonna et al. [15] used IFRT as part of CMT, studying patients with clinical stages IA-IIA favorable and unfavorable HL treated with 4 cycles of ABVD followed by either subtotal nodal irradiation or IFRT. The 12-year freedom from progression rate and OS were similar between the two study groups. Thus, 4 cycles of ABVD followed by IFRT was shown to be effective and safe in terms of toxicity and development of second malignancies for the treatment of early-stage favorable and unfavorable HL patients [15].

The EORTC H7 has study [16] randomized patients with stage I or II favorable HL to either subtotal nodal irradiation or CMT consisting of 6 cycles of EBVP followed by IFRT. The 10-year event-free survival rate was much better for the CMT compared with subtotal nodal irradiation, but the 10-year OS was once again similar between the study groups.

The EORTC/Groupe d'Études des Lymphomes de l'Adulte (GELA) H8 trial [17] randomized patients with stage I and II favorable HL to subtotal nodal irradiation or CMT using 3 cycles of the hybrid MOPP/ABV followed by IFRT. The results of this study showed once again that IFRT is a sufficient treatment after chemotherapy for early-stage favorable HL and that subtotal nodal irradiation should no longer be recommended. CMT including IFRT was associated not only with better 5-year event-free survival but also with improved 10-year OS when compared with subtotal nodal irradiation, for favorable early-stage HL. Nonetheless, the use of CMT which consists of ABVD followed by IFRT was considered to be more effective and safer in terms of toxicity and development of second malignancies than the use of extended field RT (Table 2).

Radiation therapy: new directions

As chemotherapy has become more efficient, extended RT fields have been progressively replaced by involved fields. A few years ago, the EORTC-GELA [6] radiotherapy group decided to reduce the concept of radiation field because of late complications. Cardiovascular and second cancers were correlated with the size of radiation fields. This led to the concept of involved node RT (INRT) in which only initially involved lymph nodes are irradiated [18-21].

Hodgson et al. from the Princess Margaret Hospital concluded that the effects of age at diagnosis, latency, gender, treatment and year of diagnosis are related to the appearance of secondary tumors such as breast and colorectal cancers [22]. Modern imaging techniques should be used to identify and contour involved lymph nodes with greater accuracy. PET scan helps in this matter and the modern RT technique is the intensity modulated RT (IMRT).

Table 2. Studies comparing subtotal nodal irradiation alone with combined modality therapy for favorable early-stage Hodgkin's lymphoma

Study	*Study arms*	*Median follow-up (mo)*	*FFTF (%)*	*OS (%)*
SWOG/CALGB [13]		40	3-yr FFTF	3-yr
	STNI (36-40 Gy)		81	96
	AV×3 + STNI (36-40 Gy)		94	98
GHSG HD7 [14]		87	7-yr FFTF	7-yr
	EFRT (30-40 Gy)		67	92
	ABVD×2 + EFRT (30-40 Gy)		88	94
Bonadonna et al. [15]		116	12-yr FFTF	12-yr
	ABVD×4 + STNI (30.6-40 Gy)		93	96
	ABVD×4 + IFRT (36-40 Gy)		94	94
EORTC H7F [16]		108	10-yr FFTF	10-yr
	STNI (36-40 Gy)		78	92
	EBVP×6 + IFRT (36-40 Gy)		88	92
EORTC/GELA H8F [17]		92	5-yr FFTF	10-yr
	STNI (36-40 Gy)		74	92
	MOPP/ABV×3 + IFRT (36-40 Gy)		98	97

STNI: subtotal nodal irradiation, CMT: combined-modality therapy, SWOG/CALGB: Southwest Oncology Group/Cancer and Leukemia Group B, AV: doxorubicin, vinblastine, FFTF: freedom from treatment failure, OS: overall survival, mo: months, yr: year, EFRT: extended-field radiotherapy, ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine, IFRT: involved-field radiotherapy, EBVP: epirubicin, bleomycin, vinblastine, prednisone, GELA: Groupe d'Études des Lymphomes de l'Adulte, MOPP: mechlorethamine, vincristine, procarbazine, prednisone, ABV: doxorubicin, bleomycin, vinblastine, GHSG: German Hodgkin's Study Group

IMRT technology can achieve better sparing of normal tissues compared with conventional IFRT [23, 24]. Significantly fewer late complications are expected because of limited irradiation of normal tissue. With IMRT the risk of second malignancies seems to be lower than with the extended fields, although it will take more years of careful follow-up of patients in randomized studies to display the full magnitude of risk tapering by current reduction of radiation field and dose [25-28].

The German Hodgkin Study Group (GHSG-HD)11 trial addressed two questions about how to improve the outcome by intensifying chemotherapy (ABVD × 4 vs. BEACOPP × 4) and how to define the best radiation dose (30 vs. 20 Gy IFRT). A reduction of RT dose from 30 to 20 Gy IFRT seemed to be justified only in combination with BEACOPP, but not with a less effective chemotherapy such as ABVD × 4. Patients will benefit from an intensified chemotherapy such as BEACOPP only in combination with 20 Gy IFRT but not with 30 Gy IFRT [29].

Treatment of advanced-stage disease

MOPP and ABVD were successfully used for many years in advanced-stage HL, resulting in long-term remissions of nearly 50% of the patients. Several groups tried to improve the ABVD results. These new approaches include multidrug regimens and RT [30-32].

The treatment of advanced HL is still under clinical research. A meta-analysis by Loeffler et al. reported that the comparison between the CMT and chemotherapy alone had the same tumor control but better OS for patients treated with chemotherapy alone [33]. That is why randomized trials currently evaluate the impact of RT after effective chemotherapy for advanced HL. A study conducted by the EORTC indicated that consolidation IFRT did not result in better outcome in patients who had already achieved CR after 6-8 cycles of MOPP/ABV, although RT may be beneficial to patients with PR [34].

Stanford V was developed as a short-duration, reduced-toxicity program and applied weekly over 12 weeks. Consolidation RT to sites of initial disease was employed. With an estimated 5-year freedom from progression of 89% and OS of 96%, this regimen produced very promising results. However, the data were generated at a single center [35, 36] and no confirmatory trials from other investigators were found.

All in all, patients in CR after 6-8 cycles of MOPP/ABV may not need further RT. In addition, patients with bulky disease, incomplete or uncertain CR or patients treated with brief chemotherapy schemes may benefit from IFRT to originally bulky or residual disease.

Treatment for relapsed HL

High dose chemotherapy with autologous hematopoietic stem cell transplantation is the cornerstone of

salvage therapy for most relapsed HL patients. It is also considered the standard of care for those who experience progression during remission induction.

The analysis from Stanford Hospital demonstrated that most (69%) of the relapses after autologous stem cell transplantation occurred in sites known to be involved immediately before transplantation. This was not the case when these sites had been irradiated [37].

At Memorial Sloan-Kettering Cancer Center, they provided an accelerated hyperfractionated irradiation schedule (b.i.d. fractions of 1.8 Gy each) for the salvage of relapsed HL. RT started after the reinduction chemotherapy and the stem-cell collection. An IFRT (18 Gy in 5 days) to the bulky disease was followed for patients who had not been irradiated before. An additional dose of 18 Gy (1.8 Gy per fraction, b.i.d.) was delivered to the residual disease. The patients who had been submitted to RT were given 36 Gy with involved field. The realization and the efficacy of the CMT resulted in an event free survival of 47% for the patients receiving total lymphoid irradiation (TLI) followed by cyclophosphamide-etoposide chemotherapy [38].

Various studies indicated that transplantation contributed to event free survival better than chemoradiotherapy (68 vs. 58%). Despite this, the OS rate was 88% for patients receiving chemoradiotherapy [39-41].

It is difficult to draw any conclusion about the optimal treatment strategy in advanced stages of HL. Some researchers have defined PR as a ≥50% decrease while others have used a ≥75% decrease in the product of two perpendicular diameters in all measurable and evaluable lesions, in conjunction with negative bone marrow findings, no disease symptoms and no new lesions. In addition, patients in PR after chemotherapy are often analyzed together with patients with primary progressive disease and the ones with early relapse after reaching CR with chemotherapy, with or without RT. For instance, the Groupe d'Études des Lymphomes de l'Adulte [42] has advocated high-dose chemotherapy with peripheral stem cell support for patients in PR of <75% after chemotherapy, based on their results from 157 patients with failure after induction chemotherapy (n = 67), relapse (n = 68) or PR of <75% (n = 22). We believe the conclusions of this study were unclear to advise treatment intensification for patients in PR after induction chemotherapy. Furthermore, no benefit was notice in the Intergroup HD01 trial [43] and the Scotland and Newcastle Lymphoma Group HD3 trial [44]. Additionally, high-dose chemotherapy with stem cell support is accompanied with acute treatment-related death in ≤8% of the patients [42-46]. The long-term toxicity could also be considerable [47].

Josting et al. reported on the outcome of 100 patients who were poor candidates for intensive salvage therapy and who had limited stage disease at relapse. They were treated with salvage RT after first relapse of HL [48]. The response rate was 81% (77% CR) and 5-year FFTF and OS were 28 and 51%, respectively.

McDonald et al. examined the relapse patterns and outcomes of patients with early stage HL who relapsed after initial therapy with ABVD +/− extended field RT [49]. Among 24 patients who relapsed after treatment with 4-6 cycles of ABVD alone, 14 patients were treated with salvage therapy that included RT. Seventy-five percent of relapsed patients survived without a new progression.

New agents

Recent studies also included exploitation of the expression of CD30 on the Reed-Sternberg cells. Antibodies targeting this molecule had shown promise *in vitro*. Recent trials of SGN-30 (humanized antiCD30 mouse monoclonal antibody) and MDX-060 (fully humanized antibody) showed few side effects, however, only limited clinical response was seen. Other areas of interest include immunotoxins directed against CD25, as well as immunotherapy with cytotoxic T-cells targeting Epstein-Barr virus antigens as well as the Reed-Sternberg cells [50-53].

Antibody therapy directed toward CD20 may have a role in HL, perhaps by targeting the non-malignant B-cells which support the Reed-Sternberg cells. Younes et al. treated 22 patients with recurrent nodular sclerosing HL with 6 weekly doses of the anti-CD20 antibody rituximab [54]. Twenty-two percent of patients responded, with a median response duration of 7.8 months. Responses were independent of CD20 status and were limited to patients without extranodal involvement. Six of 7 patients had resolution of B symptoms. The same group has also combined rituximab with chemotherapy in patients with relapsed HL [55]. Thirteen of 26 heavily-pretreated patients, none of whom had extranodal disease, responded to a combination of rituximab and gemcitabine. Galiximab is a primatized monoclonal antibody directed against CD80, an immune costimulatory molecule that regulates T-cell functions via interaction with CD28. Galiximab is well-tolerated; its primary toxicity is infusion reaction. CD80 expression has been demonstrated on Reed-Sternberg cells, providing a rationale for treatment of HL with galiximab [56].

Discussion

The impact on OS of different treatment ap-

proaches used in prospectively randomized studies has always been very hard to demonstrate in HL because disease control and early toxicity estimations often guided the evolvement of current treatment strategies [57-59]. In most HL studies, the number of patients and the number of events, especially in early-stage disease, are small and therefore no statistical conclusions can be drawn. The control of advanced disease through one approach of treatment may ultimately increase toxicity and be more threatening for the patient's life than the disease itself. For these reasons, adding RT or reinforcing chemotherapy is an alternative option. Finally, most studies are reported early, often without full peer-review and detailed analysis of events and many large cooperative group studies do not have optimal follow-up and information on the cause of death. It may be misleading to declare an equality of two treatment options because they lack an OS difference and they ignore the improved FFTF even if it is vital.

As expected, when comparing patients in PR after chemotherapy who received RT with the ones in CR, significantly more patients with bulky (mediastinal) disease at the start of treatment are to be found in the PR group. However, the only factor associated with the final treatment outcome was the response to RT. Obviously, we need other, probably biologic, parameters to predict the treatment outcome [60-65].

Despite the abundance of guidelines for the treatment of HL, individualization of treatment must be taken for granted when a particular treatment approach might avoid a high risk for a serious late complication, even if this complication may not influence OS. Patients' preferences must be taken into account. As therapy of HL evolves, it is imperative to continue the long-term follow up of survivors with careful documentation of late effects associated with new treatments. Analysis of randomized studies supports the inclusion of reduced-field and dose of RT in treatment strategies for HL.

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