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The EORTC Trials for Limited Stage Hodgkin's Disease

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SINCE 1964, all the efforts of the Lymphoma Group of the EORTC (European Organisation for Research and Treatment of Cancer) have been devoted to the task of tailoring treatment to the presentation of Hodgkin's disease (HD) for any given patient [1–12].

We will first briefly review the results of the four controlled studies conducted by the group from 1964 to 1988 for stages I and II HD.

We will then present in detail the designs of the on-going H7 randomised trials for these same subsets of Hodgkin's disease patients.

THE H_1 TRIAL (1964–1971)

It included 288 patients with supradiaphragmatic stage I–II HD; actually, few cases of infradiaphragmatic limited stage HD patients were enrolled in the study [12] (of note, infradiaphragmatic presentations were systematically excluded from all the subsequent EORTC studies).

No laparotomy was performed at that time. Mantle field radiotherapy (RT) (or inverted Y RT) was considered to be the main therapy. The question that was asked in 1964 was: "Could a monochemotherapy—namely, weekly Velban for 2 years—improve the results achieved by regional irradiation alone?". All patients received first a regional RT (mantle field irradiation or inverted Y). They were then randomly assigned to one of two groups: (a) no further treatment, or (b) a weekly injection of Velban (VLB) for 2 years.

The 15-year results show a definite advantage of combination RT-VLB over RT alone in terms of disease-free survival (DFS): 60% for RT-VLB vs. 38% for RT alone ($P < 0.001$). However, this DFS advantage was not translated into any survival benefit; 15-year survival rate was 65% for RT-VLB and 58% for RT alone [non-significant difference (NS)] [8]. These findings suggest that salvage treatment was more efficient in the RT alone group than in the group of patients who had received the RT-Velban association.

In addition, the incidence of relapse in the unirradiated para-aortic (PA) region was high, strongly suggesting a need to explore and/or to systematically treat this area.

THE H_2 TRIAL (1972–1976)

It included 300 patients with supradiaphragmatic stages I or II HD. The trial was designed on the basis of the preliminary results of the H_1 trial and of the data which were available in the literature at that time[6].

In 1972, the evaluation of staging laparotomy and splenectomy could hardly be avoided. As mentioned above, the preliminary data from the H_1 trial indicated that the paraaortic region should be either explored or treated. Thus patients were randomised to undergo either: (a) staging laparotomy and splenectomy, followed by mantle field RT and para-aortic RT, or (b) mantle field RT, then para-aortic (PA) and spleen RT (subtotal nodal irradiation: STNI). The trial actually compared splenectomy and splenic irradiation but also permitted an assessment of the prognostic significance of the information provided by the exploratory laparotomy.

In addition, based on preliminary data drawn from the H_1 trial, patients with mixed cellularity (MC) or lymphocytic depletion (LD) histologic subtypes were randomly assigned to (a) VLB alone or (b) VLB + procarbazine, for 2 years.

At 12 years, the DFS was 68% for STNI alone, and 76% for laparotomy-STNI (NS). Survival was 77% for STNI, and 79% for laparotomy-STNI (NS)[8].

A positive laparotomy was very predictive for subsequent relapse; after a negative laparotomy (lap−) the 12-year DFS rate was 83% while it was only 56% after a positive exploration (lap+) ($P < 0.001$). However, this advantage did not turn out to yield any benefit in terms of survival; 80% for lap−, 76% for lap+ (NS), at 12 years, probably due to salvage treatment efficacy.

Patients with MC and LD histological subtypes who received chemotherapy (CT) experienced a better DFS (85% at 12 years) than patients who were not given any CT (65% DFS) ($P < 0.001$). However, no difference in survival rates could be detected between the two groups of patients; 75% for the CT group, 80% for the no-CT group at 12 years (NS) [8].

THE H_5 TRIALS (1977–1982)

A total number of 494 patients with stages I or II supradiaphragmatic HD [2] was enrolled in these trials. To further adapt the management strategy, two groups, favourable and unfavourable were selected, according to prognostic indicators which were drawn from a preliminary analysis of the combined H_1 and H_2 trials (details in [1]).

For patients in the favourable group it was postulated that a limited treatment (RT alone) could be considered once definite evidence of non-infradiaphragmatic involvement was obtained. All patients in this group (trial H5–F) first underwent a laparotomy and splenectomy. If negative, the patients were randomly assigned to (a) mantle field irradiation alone, or (b) mantle RT + PA irradiation.

If the laparotomy detected an abdominal extension of the disease, the patients were referred to the unfavourable trial (H5–U) (see infra).

In the favourable subgroup (negative laparotomy) the 9-year DFS was 69% for mantle RT, and 70% for mantle + PA RT

*See Appendix.

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(NS). 9-year survival rates were 94 and 91%, respectively, in the two subsets (NS).

Therefore, for patients with initial favourable prognostic indicators and without any infradiaphragmatic extension (based on laparotomy findings), the addition of a para-aortic irradiation did not yield any benefit, either in terms of disease-free survival or in terms of overall survival. Moreover, supplementary irradiation after laparotomy could have been responsible for additional small bowel and gastric toxicity[13].

In patients with unfavourable indicators at onset, laparotomy was not performed since extensive treatment was thought to be necessary anyway. Together with patients with favourable initial prognostic indicators but with laparotomy-proven infradiaphragmatic extension, they were included in the so-called H5-U trial. Patients were randomly assigned to either (a) total nodal irradiation (TNI), or (b) combined modality treatment: 3 MOPP-mantle RT-3 MOPP. 9-year DFS rate was significantly better in the combined treatment group: 83 vs. 66% for TNI ($P < 0.001$). However, overall results for survival only showed a borderline advantage for MOPP–RT–MOPP; 88 vs. 73% for TNI ($P = 0.06$). In patients below 40 years of age, no difference in long-term survival could be detected between MOPP–RT–MOPP and TNI [1, 8].

THE H_6 TRIALS (1982–1988)

They included 559 patients with stage I–II supradiaphragmatic Hodgkin's disease. The analysis of the previous trials allowed further refinements of prognostic factors, and patients were selected on this basis to be entered in a favourable (H6–F) or unfavourable (H6–U) trial [2].

The H6–F trial addressed the question of the need of laparotomy and splenectomy for this group of patients. In a first arm (a) the patients underwent a laparotomy, followed by a treatment which was adapted to the pathology findings; if lap−, mantle field RT (+ PA if MC or LD histologic subtypes) was administered while in case of lap+, a combination of CT–RT (see unfavourable subgroup below) was given.

In the second arm (b) patients without any prior surgical exploration, directly received mantle RT, and then para-aortic + spleen RT (STNI).

In this pragmatic trial, aiming at evaluating the long-term usefulness of laparotomy, the end-point was survival and not DFS. At 5-year follow-up, DFS was significantly lower in the STNI group (79%) than in the laparotomy (+ adapted treatment) group (89%) ($P = 0.02$), as expected. However, due to the efficacy of salvage procedures, 5-year survival rate was similar in the two groups; 94% for STNI, 90% for laparotomy and adapted treatment (NS).

The unfavourable trial H6–U was based on the preliminary results of the H5–U trial, which showed a significant advantage for the CT–RT combination over TNI in terms of DFS.

In this trial, patients were randomly assigned either to (a) 3 MOPP, mantle RT–3 MOPP, or to (b) 3 ABVD–mantle RT–3 ABVD [14, 15]. At 5 years, DFS was significantly lower in the MOPP group (79%) than in the ABVD group (89%) ($P = 0.02$). Nevertheless, there was no difference in survival [MOPP : 88%, ABVD: 89%(NS)]. One of the main points of interest will be the evaluation of treatment-related toxicity in the two arms. This evaluation could be performed prospectively in a large proportion of patients. Preliminary data suggest that early pulmonary toxicity could be increased in the ABVD-RT arm of the study [16]. However, it would be premature to draw firm conclusions on late toxicities at this point in time.

THE ON-GOING H_7 TRIALS (ACTIVATED IN NOVEMBER 1988)

As for the work-up strategy, the EORTC Lymphoma Cooperative Group decided to give up using systematic laparotomy for stage I–II supradiaphragmatic Hodgkin's disease [8, 17, 18]. In this line the on-going H7 trials are only dealing with clinically staged (CS) limited HD patients. They are based upon the data obtained from the previous EORTC studies as well as upon recent results published in the literature [19–27].

The H_5 studies are asking specific questions for three well defined groups of patients.

The very favourable subgroup (H7-VF)

Such a subgroup of patients is seldom individualised in the current protocols. However, most trained HD specialists recognise that there is a small subset of patients with very benign presentation, for whom staging and treatment could safely be limited.

Turning to the EORTC database, the Lymphoma Cooperative Group tried to identify a subgroup of patients which could be safely proposed a minimal treatment, i.e. mantle field irradiation alone. These patients would secondarily be spared the untoward effects of laparotomy, chemotherapy and extended field irradiation. Actually, the EORTC data indicated that only a very small subset of patients could be proposed such a limited irradiation as the sole treatment. This subgroup is very restrictively defined, only including patients with CS I, below 40 years of age, without any systemic symptom and with erythrocyte sedimentation rate (ESR) less than 50 mm (first hour), of female gender, of lymphocytic predominance or nodular sclerosing histological type and without bulky mediastinal involvement. This subgroup only represents 6% of the total number of CS I–II supradiaphragmatic HD in the EORTC experience.

These patients are therefore currently proposed a mantle field irradiation alone. The small number of patients to be included in this study does not permit randomisation. The relapse rate is expected to be low, less than 10%, and these rare relapses are expected to be easily salvaged in these non-aggressively-treated patients. However, careful long-term follow-up will be necessary, in order to detect possible late relapses.

The unfavourable subgroup (H7-U)

At the other end of the spectum, there is a general agreement to consider that the clinical presentation of some patients is so severe that: (1) laparotomy is not useful, since it would not change a therapy which should be aggressive anyway (see supra); and (2) chemotherapy is mandatory treatment.

Based on the analysis of the data drawn from the previous trials, the EORTC Lymphoma Cooperative Group defined an unfavourable group which comprises about 40% of the patients. The presence of only one of the following prognostic factors is sufficient for a patients to be included in this group: age over 50 years; no B symptoms with ESR >50 (or presence of B symptoms with ESR >30); 4 (or more) involved sites (i.e. CS II_4 or more); bulky mediastinal involvement (M/T ratio > 0.35). For these patients, the data gathered by the EORTC as well as by other groups, clearly indicate that a combination of chemotherapy and radiotherapy is superior to radiotherapy alone for long-term survival.

The still unsolved problem is to find out what would be the best combination considering not only response rate, but also late toxicity, fertility [28, 29], secondary cancers [30–34], etc. In the ongoing H7–U trial, it was decided that the following

two schedules be compared: (1) six cycles of EBVP II (a combination of epirubicine, bleomycine, vinblastine and prednisone [35, 36] followed by an irradiation limited to the initially involved fields; and (2) six cycles of MOPP/ABV (according to the conventional scheme [37, 38]) followed by the same type of radiotherapy.

Relapse and survival rates, but also acute and late toxicities, are to be carefully evaluated in both arms of the trial.

The favourable subgroup (H7–F)

It includes all the patients who were not entered in the previous two groups. It represents about 54% of the patients in the EORTC experience. For this group, the analysis of the EORTC database showed a significant advantage of the chemotherapy–radiotherapy combination over radiotherapy alone in terms of disease-free survival. However, similar and satisfactory long-term survival rates were achieved by both modalities. Therefore, only a difference in toxicity (mostly long-term toxicity) would result in preference given to one of these two treatment strategies.

Two treatment arms are to be compared: (a) subtotal nodal radiotherapy (mantle field, then para-aortic and spleen irradiation), without any chemotherapy, and (b) six courses of EBVP II (see above) followed by the irradiation of the initially involved fields. Acute and late treatment toxicities are carefully and prospectively recorded in both arms of this control study.

CONCLUSION

Long-term survival rates, superior or close to 90%, are at hand for most of the patients presenting with clinical stage I–II supradiaphragmatic Hodgkin's disease. Beside the necessary efforts to improve the outcome of the few patients still failing our primary treatments, our energy should now be devoted to the reduction of long-term toxicity [39–43]. The current EORTC H7 trials, which are reserving aggressive (and potentially toxic) treatment to well-defined unfavourable situations, and which are trying to lighten the burden of the therapy for low-risk patients, are keeping in line with this objective.

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APPENDIX

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