RELAPSE PATTERNS IN EARLY-PET NEGATIVE, LIMITED-STAGE HODGKIN LYMPHOMA (HL) AFTER ABVD WITH OR WITHOUT RADIOTHERAPY–A JOINT ANALYSIS OF EORTC/LYSA/FIL H10 AND NCRI RAPID TRIALS

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Abstract

In H10 and RAPID randomized trials, chemotherapy+radiotherapy (combined modalities, CMT) was compared with chemotherapy (C) in limited-stage Hodgkin lymphoma (HL), with negative early-PET (ePETneg). We analyzed patterns of relapses in H10, validated findings in RAPID and performed a combined analysis stratified by trial.

Impact of radiotherapy (RT) on risk of relapse was studied with adjusted Cox models with time-varying effects.

In H10, 1059 ePETneg pts were included (465 EORTC favourable (F), 594 unfavourable (U)). Among F, 2/227 (1%) relapsed after CMT, 30/238 (13%) after C: 21/30 (70%) <2yrs, 25/30 (83%) in originally involved areas. Among U, 16/292 (5%) relapsed after CMT, 30/302 (10%) after C: 8/16 (50%) vs 27/30 (90%) <2yrs, and 11/16 (69%) vs 26/30 (87%) affecting originally involved areas.

Similar results were observed in 419 ePETneg RAPID pts (241 F, 128 U, 50 unclassified): in F, 6/118 (5%) relapsed after CMT; 13/123 (11%) after C: 11/13 (85%) <2yrs, 11/13 (85%) affecting originally involved areas. In U, 3/65 (5%) relapsed after CMT, 5/63 (8%) after C.

In both trials, omitting RT in ePETneg HL resulted in more early relapses, mainly affecting originally involved areas. RT significantly reduced risk of early relapses in the combined stratified analysis.

Keywords: Hodgkin Lymphoma, relapse, early PET, chemotherapy, radiotherapy

Short Title: Relapses in early-PET negative limited-stage Hodgkin lymphoma

Introduction

Rates of long-term cure for limited stage classical Hodgkin lymphoma (HL) currently exceed 90%, with the use of multiagent chemotherapy followed by radiotherapy (combined modalities treatment, CMT)[1-3] albeit at the cost of long-term side effects, mainly second malignancies and cardiovascular events due to radiotherapy (RT)[4-6]. Optimized baseline prognostic factors and early predictors of relapse would be of great clinical importance for balancing early cure rates and risk of long-term sequelae.

Early assessment with PET (early PET- ePET) has been shown to be an important predictor of outcomes, in both limited and advanced stage HL [7-11]and response-adapted treatments have been the focus of several trials.[12-16]

The randomized-controlled EORTC-LYSA-FIL H10 and NCRI RAPID trials were designed to establish whether RT could be safely omitted in newly diagnosed limited-stage HL patients who were early PET-negative (ePETneg) after 2 (H10) or 3 (RAPID) cycles of ABVD[17,18]. Both studies could not demonstrate the non-inferiority of a chemotherapy-only (C) approach. Relapses occurred more frequently in patients treated with C, even when ePET was negative.

The aim of this project was to explore the relapses in ePETneg patients, describing their timings and sites and impact of baseline clinical factors on the risk of relapse. Such information could help tailor the follow-up of patients treated for limited-stage HL and identify those who are at higher risk of relapse, despite being ePETneg. We first conducted the analysis in the H10 cohort, then we sought to validate our findings in the comparable and independent RAPID dataset. Lastly, we performed a combined analysis stratifying by trial.

Patients and Methods

Eligibility Criteria

The EORTC-LYSA-FIL 20051 H10 trial included patients aged 15-70 with untreated stage I/II HL. Patients were stratified as favourable (F) and unfavourable (U) according to EORTC criteria (U: at least one of the following: age≥50 years, >3 nodal areas or mediastinal-thoracic ratio≥0.35, no B symptoms and erythrocyte sedimentation rate (ESR) ≥50 or B symptoms and ESR ≥30. F: not fitting U criteria).

The NCRI RAPID trial enrolled patients aged 16-75 with untreated stage I/IIA HL. Patients with B-symptoms and/or mediastinal bulk (defined as maximum mediastinal diameter ≥33%) were excluded.

Treatment

In H10, patients were randomized upfront to standard or experimental arms. Early PET was performed after 2 x ABVD. Standard CMT consisted of ABVD x3 (F) or ABVD x4 (U) and involved-node RT, irrespective of ePET result. In the experimental arm, ePETneg patients after 2 x ABVD received chemotherapy (C) with 2 (F) or 4 (U) further cycles of ABVD.

In RAPID, all patients received 3 x ABVD, followed by ePET. Patients with negative ePET were randomized to 30-Gy involved-field RT or no further treatment.

Figure 1 shows the treatment scheme in the two trials.

Early PET scans

In H10 ePET scans were scored according to International Harmonisation Project (IHP) criteria (the standard at the start of the trial): lesions ≥2cm in diameter were considered positive if uptake was higher than the mediastinal blood pool, lesions <2cm were considered positive if uptake was higher than the surrounding background.[19]

RAPID used the Deauville 5-point scale and a score of 1 (no uptake) or 2 (uptake ≤ mediastinal blood pool) was considered negative, a score of 3-5 positive.[20]

Statistical Analysis

The analysis is mainly descriptive. We first investigated the pattern of relapses in the H10 trial. Time to relapse was defined as the interval between randomization and relapse. Patients who died without evidence of relapse were censored at time of death but were not treated as competing risk events. Early relapses are generally defined as occurring within either 1 or 2 years after completion of treatment; we used a cut off of 2 years from randomization. Site of relapse was defined as affecting "originally involved areas", irradiated or not, "originally uninvolved areas" or "originally involved and originally uninvolved areas". Data is presented in frequency tables.

One multivariable Cox model adjusted for baseline characteristics was used to estimate the hazard ratio (HR) of RT vs no RT, its 95% confidence interval (CI) and p-value. In H10, baseline characteristics were age, gender, stage, histology, B-symptoms, number of involved areas, ESR and mediastinal bulk. The proportional hazard (PH) assumption was checked and the hazard was plotted over time to understand any potential time-dependency[21](Supplementary Figure 1). As there was evidence of non-PH for the

treatment effect, one model with time-varying hazard ratio for treatment effect (<2 years vs ≥2 years) and adjusted for the same baseline characteristics was used.

To externally validate findings from H10, we repeated the analysis in RAPID. Patients were assigned retrospectively to F or U prognostic groups according to the EORTC criteria. As RAPID did not include patients with bulk and/or B symptoms, the number of U patients was small, and so were relapses. This prevented a reliable comparison with the H10 U counterpart. Moreover, due to differences in inclusion criteria and smaller numbers, the Cox model in the RAPID trial was only adjusted for age, gender, histology and stage.

Finally, as the results from the two trials showed similar effects of RT on the time to relapse, data were combined in an analysis stratified by trial. In addition to adjusting for age, gender and stage, this Cox model was stratified by trial to account for differences between the two studies.

Additional un-planned analyses to investigate the potential predictive value of the baseline characteristics were carried out, although no formal analysis of interaction was possible due to lack of statistical power. These exploratory descriptive analyses were conducted by displaying Kaplan-Meier curves of progression-free rates (PFR) by RT and each level of the baseline characteristics. Rates at 5 years were estimated with corresponding 95% CIs.

All statistical tests were conducted at the two-sided 0.05 significance level. All analyses were performed with SAS software, version 9.4 (SAS Institute).

Results

Timing of Relapses

Details of early and late relapses and PFR curves are detailed in Table 1 and Figure 2.

In H10, 1059 ePETneg patients were included. With a median follow up of 5.1 years, calculated using the reverse Kaplan-Meier curve of overall survival, 78/1059 (7%) patients relapsed: 18/519 (3%) relapsed after CMT, 60/540 (11%) after C. Among the 465 F patients, 2/227 (1%) relapsed after CMT, one <2yrs; 30/238 (13%) relapsed after C of which 21/30 (70%) within 2 years. The 5yrs PFR was 99% (95% CI: 96-100%) after

CMT and 88% (95% CI: 83-91%) after C. Among the 594 U patients, 16/292 (5%) relapsed after CMT, 8 (50%) <2yrs; 30/302 patients (10%) relapsed after C, 27/30 (90%) within 2 years. The 5yrs PFR were 94% (95% CI: 90-96%) for CMT and 90% (95% CI: 86-93%) for C.

In RAPID, 419 patients were ePETneg. With a median follow up of 5.2 years, 30/419 (7%) relapsed: 9/208 (4%) after CMT and 21/211 (10%) after C. Fifty/419 (12%) patients could not be assigned to F or U, mainly due to lack of ESR values. Among the 241 F patients, 6/118 (5%) relapsed after CMT, 13/123 (11%) after C; of these relapses, 11/13 (85%) occurred within 2 yrs in C, and 2/6 (33%) in CMT. The 5yrs PFR was 94% (95% CI: 90-96%) after CMT and 90% (95% CI: 86-93%) after C. Only 128 patients were categorized as U in RAPID: 3/65 (5%) patients relapsed after CMT and 5/63 (8%) after C, with 5yrs PFR of 93% (95% CI: 80-98%) and 92% (95% CI: 80-97%), respectively.

Sites of Relapses

Sites of relapses are detailed in Table 1.

In H10, after CMT, in F patients there were no relapses restricted to originally involved areas, one relapse affecting originally involved and originally uninvolved areas and one affecting originally uninvolved areas only. In U patients, 11/16 relapses (69%) affected originally involved areas, of which 5/16 (31%) were confined to originally involved areas.

Relapses after C mostly affected originally involved areas both in F and U patients: 25/30 (83%) and 26/30 (87%) respectively. Relapses were confined to originally involved areas in 22/30 (73%) in F and 20/30 (67%) in U patients, while 3/30 relapses (10%) in F and 6/30 relapses (20%) in U patients affected originally involved as well as originally uninvolved areas.

In RAPID F, after CMT, there were 4/6 (67%) relapses affecting originally involved areas, 1 of which confined to originally involved areas.

After C, 11/13 (85%) relapses affected originally involved areas, 6 of which were confined to originally involved areas.

Effect of RT and baseline characteristics on timing and risk of relapse

Results are summarized in Figure 3 and Table 2.

In H10, the Cox proportional hazard models adjusted for baseline characteristics included 1023 ePETneg patients (after excluding 27 patients with unclassifiable HL subtype, 5 incorrectly enrolled with stage III/V, 2 with missing values for mediastinal size and 2 patients with missing ESR values) with a total of 71 events observed. The adjusted risk of relapse was significantly lower in CMT than in C during the first 2 years (adjusted HR=0·21, 95% CI: 0·10-0·43, p<0·001), but not afterwards (adjusted HR=0·76, 95% CI: 0·32-1·84, p=0·545).

In H10, the following were independent prognostic factors: gender (HR (female versus male) = 0·42, 95% CI: 0·25-0·69, p<0·001), Ann Arbor stage (HR (stage II versus I) = 2·37, 95% CI: 1·11-5·06, p=0·025) and histology (HR (Mixed Cellularity or Lymphocyte Depleted versus Nodular Sclerosis or Lymphocyte Rich) = 2·01, 95% CI: 1·08-3·75, p=0·029). The presence of a bulky mediastinal mass or B symptoms, age, number of nodal areas, ESR did not show a significant prognostic effect on the risk of relapse in the multivariate analysis.

In RAPID, all 419 patients were included in the multivariate model, with 30 events observed. Results in this dataset externally validated the findings of the association with RT from the H10 trial: the effect of RT was statistically significant and of similar magnitude during the first 2 years (adjusted HR=0·19, 95% CI: 0·06-0·65, p=0·008); after 2 years, the observed adjusted HR was close to 1 (adjusted HR=1·07, 95% CI: 0·32-3·53, p=0·914).

In RAPID, no strong evidence for prognostic baseline factors was observed. The effects for gender (HR (female versus male) = 0·72, 95% CI: 0·35-1·50, p=0·378) and stage (HR (stage II versus I) = 1·24, 95% CI: 0·56-2·79, p=0·596) were in the same direction as the H10 trial, but due to the low number of events, confidence intervals were wide.

As the effect of RT was similar in both studies, data were combined in an adjusted Cox model stratified by trial. In the combined dataset, the observed HR for relapses in the CMT cohort, compared to C, was 0.20 (95% CI: 0.11-0.37, p<0.001) in the first 2 years, and 0.84 (95% CI: 0.41-1.69, p=0.618) after 2 years. As expected, the prognostic effect of gender and stage remained statistically significant in the combined stratified analyses, as the results were mainly driven by H10.

Exploratory predictive analysis for differential treatment effects of baseline characteristics on the risk of relapse

In this additional exploratory part of the project, the prognostic significance of the variables RT and each level of the baseline characteristics were analyzed using Kaplan-Meier method. The PFR curves are shown in Supplementary Figure 2.

In H10, Kaplan Meier curves suggest that age, gender and number of nodal areas involved may have an influence on treatment effect. Males seem to benefit more from RT (5yr PFR 95% in CMT vs 84% in C) than females (5y PFR 97% in CMT vs 93% in C). Patients over the age of 50 (5yr PFR 95% in CMT vs 94% in C) seem to benefit less from RT, compared to younger patients (5yr PFR 96% in CMT vs 88% in C). Finally, patients with ≤3 nodal areas involved (5yr PFR 97% in CMT vs 89% in C) appear to benefit from RT, while patients with > 3 do not (5yr PFR 87% in CMT vs 88% in C).

In RAPID, because of smaller patient numbers and fewer events, it is even more difficult to draw reliable conclusions about the predictive value of the baseline characteristics. Nonetheless, as in H10, male patients and younger patients seem to benefit more from RT than female patients or older patients, respectively.

Due to lack of power, the potential predictive value of the baseline characteristics could not be assessed through formal interaction analyses. Overall, these results need to be interpreted with caution, as the analyses are exploratory, and the number of events is small.

Discussion

This project is the result of an international collaboration between the EORTC/LYSA/FIL and the UK NCRI Groups. This collaboration allowed us to externally validate the findings from the H10 trial, in the comparable independent RAPID dataset.

The overall risk of relapse in patients with limited stage HL achieving an ePETneg status after 2-3 cycles of ABVD was low (7%) in both trials.

Risk of relapse was lower in patients treated with CMT (3% in H10 and 5% RAPID) compared to C (11% in H10, 10% in RAPID) after a median follow-up of more than 5 years. When we separately analyzed the EORTC/LYSA/FIL H10 and RAPID cohorts by EORTC prognostic groups (F and U), differences in 5yrs PFR in ePETneg patients between CMT and C only group were as follows: 99% vs 88% in the H10 F group, 94% vs

90% in the RAPID F group, 94% vs 90% in the H10 U group and 93% vs 92% in the RAPID U group, respectively. Remarkably, very similar results have been reported recently from the HD16 trial in limited-stage favourable German Hodgkin Study Group (GHSG) patients (similar to EORTC F category) with 93% vs 86% 5yr PFS respectively for CMT vs C.[11] It is worth noting that, in the HD16 trial, ePET negative patients received a shorter treatment, consisting of either 2xABVD + 20Gy IF-RT in the CMT arm, or 2xABVD in the C arm.

In the H10 F cohort, most relapses after C occurred within 2yrs (21/30; 70%) and this was also observed in RAPID (11/13; 85%). Results were similar in the H10 U cohort: 27/30 (90%). Due to the differences in inclusion criteria, the small number of patients classified as U in the RAPID dataset (63 C, 65 CMT) did not allow for any reliable comparison between studies in this subgroup, with very few relapses observed (n=3 within 2 yrs and n=2 after 2 yrs in C).

In support of these observations, RT significantly reduced the risk of relapse in the first 2 years (HR in the combined stratified analysis 0·20, 95% CI: 0·11-0·37), but not after (HR 0·84, 95% CI: 0·42-1·69). This finding was consistent in the separate analyses of each trial. The main objective of both trials was to evaluate whether C was non-inferior to CMT in terms of risk of relapse in ePETnegative pts. In the statistical design of both trials a non-inferiority threshold of difference in relapse risk of 7-10% was defined. This was based on literature data of incidence of late events, as to compensate a presumed increased risk of relapse after C by the increased risk of late long-term side effects after CMT. The non-inferiority of C could not be demonstrated mainly because of the increased relapse risk after C in the first 2 years post-treatment. Whether the increased risk of early relapse after C will translate in improved long-term survival through the presumed lower incidence of long-term side effects has to be determined after prolonged observation periods, that are not available yet.

In the H10 F cohort most relapses after C were confined to originally involved areas, while in RAPID this pattern was less pronounced. Whether the difference in study protocol treatment, in which additional chemotherapy was given in H10 to ePETneg C pts, whereas in RAPID no further treatment was given, is speculative. In U patients the risk of relapse after C was still higher than after CMT, but the difference was not as marked, due to rather “delayed” relapses after CMT and a high number of relapses occurring in irradiated sites in patients receiving CMT. In H10, U patients assigned to C received 6 cycles of ABVD chemotherapy, while patients assigned to CMT received 4: one possible explanation is that more advanced disease, possibly reflecting more “widespread” disease, could benefit from more effective

systemic therapy rather than local RT. Due to the smaller numbers of U pts in RAPID trial, these findings could not be validated in the RAPID cohort.

Taken together, these results show that, in ePETneg patients, relapses occur more often after C than after CMT and they occur early after treatment, particularly in F patients. A high proportion of relapses occur in originally involved areas, strongly suggesting that local residual disease remained despite the ePETneg status. Salvage treatment was not standardized in either trial and It was left to the discretion of the treating physician. Although data on salvage treatment are being collected, a formal complete analysis has not yet been performed, so It is not possible to comment on the efficacy of the kind of salvage treatment.

The second part of the project explored whether any baseline factors were associated with the observed higher risk of relapse when RT is omitted. This was a post-hoc analysis, and, as such, only hypothesis generating. Our data suggest that RT may have a more pronounced effect on reducing the risk of relapse in males compared to females. This difference was less pronounced in the RAPID cohort. Caution should be advised in interpretation of these data and because of the relatively small numbers of events and pts in the different subgroups, we decided not to perform a statistical significance test. While no definitive conclusions can be drawn, this finding could be of clinical interest and subject of further investigations.

This project has limitations: it is a retrospective analysis, albeit from two large phase III randomized-controlled trials. Differences in inclusion criteria prevented a more in-depth comparison of the U groups. The analysis of the impact of treatment and baseline characteristics on the risk of relapse was an exploratory post-hoc analysis. The small number of relapses resulted in limited power for this analysis: therefore, the predictive value of baseline characteristics could not be reliably evaluated.
Long-term follow-up will reveal whether the increased risk of early relapses after C is balanced by a lower risk of late secondary events.
A key strength of this study is that the analyses initially conducted in H10 were externally validated in the independent and comparable RAPID trials dataset. Even in ePET neg patients, relapses were more frequent after C than after CMT, most occurred <2yrs and affected originally involved areas. RT significantly reduced the risk of early relapses.

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Conflict of Interest:

No relevant conflicts of interest to disclose.

Authorship Statement:

VF,CF,IA,AN,MA,MF,JRaemaekers designed the research project; CF, AN, LCH, NC conducted the statistical analysis; all authors reviewed the results and contributed to data interpretation; VF, AN, CF, JRaemaekers wrote the manuscript; all authors critically reviewed, commented and approved the final manuscript.

Data Availability Statement:

Data will be shared according to each consortium's policy:

For H10, please refer to EORTC data release policy (https://www.eortc.org/data-sharing/)

For RAPID, please refer to http://www.ctc.ucl.ac.uk/DataSampleSharing.aspx

Informed Consents and Clinical Trial Registrations:

No additional consenting was needed for these projects as no additional data was collected; for original consents and ethical approvals details please refer to the original publications (Andre et al, JCO 2017; Radford et al, NEJM 2015).

Clinical Trial Registration: NCT00433433; NCT00943423

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