Rider et al. Int J Blood Res Disord 2015, 2:2
ISSN: 2469-5696

International Journal of
Blood Research and Disorders

Research Article: Open Access

The Role of Positron Emission Tomography Imaging in the Risk-Adapted Treatment of Stage I-II Hodgkin's Lymphoma - A Retrospective Analysis

Tom Rider[1], John Jones[2], John Brewin[1], Gillian Horne[1], Jack Wills[1], Hannah Barton[1], Kevin Boyd[2], Timothy Corbett[2], Sabina Dizdarevic[1] and Timothy Chevassut[1,2]*

[1]*Brighton and Sussex Medical School, University of Sussex, UK*

[2]*Royal Sussex County Hospital, Eastern Road, UK*

***Corresponding author:** *Dr. Timothy Chevassut, MA, FRCP, FRCPath, PhD, Medical Research Building, Brighton and Sussex Medical School, University of Sussex, Falmer, East Sussex, Brighton, BN9 1PS, UK, Tel: 01273 873232, Fax: 01273 664837, E-mail: t.chevassut@bsms.ac.uk*

Abstract

Early stage Hodgkin's Lymphoma (HL) has excellent outcomes and recent research has focused on minimising treatment-related toxicities. However, the role of 18F-fluorodeoxyglucose positron emission tomography (FDG PET) imaging in this setting is not fully determined. We retrospectively calculated overall survival (OS) and relapse free survival (RFS) in stage I-II HL when radiotherapy was omitted if post-chemotherapy FDG PET imaging was negative.

In total 36 Ann-Arbor stage I-II patients were identified who had FDG PET assessment following chemotherapy. The median age at diagnosis was 38 and 58% were female. The mean number of cycles of chemotherapy given was 4.5 and the mean duration of follow-up was 96 months. Of the 36 patients 35 had complete response (CR) and 1 had partial response (PR). Radiotherapy was only administered to the patient in PR post-chemotherapy.

No relapses occurred during the follow-up period in the patients with CR post-chemotherapy; this group had radiotherapy omitted. The PR patient relapsed twice in total despite receiving radiotherapy in addition to chemotherapy. No deaths occurred during the follow-up period (OS 100%) and the RFS was 97.8%.

Our data indicate that radiotherapy can be safely omitted when the post-chemotherapy FDG PET scan is negative in early stage Hodgkin's lymphoma without compromising outcome, thereby sparing the patient the toxicity and potential late side-effects of radiotherapy treatment.

Keywords

Hodgkin's lymphoma, Staging, Radiotherapy, Chemotherapy, Positron emission tomography, FDG PET

Abbreviations

HL: Hodgkin's Lymphoma, FDGPET: 18F-fluorodeoxyglucose Positron Emission Tomography, OS: Overall Survival, RFS: Relapse Free Survival, CT: Computerised Tomography, CR: Complete response, PR: Partial Response, CMT: Combined Modality Therapy, PD: Progressive Disease, ABVD: Doxorubicin/Bleomycin/Vinblastine/Dacarbazine Chemotherapy, EBVP: Epirubicin/Bleomycin/Vinblastine/Prednisolone Chemotherapy, BEACOPP: Blemoycin/Etoposide/Adriamycin/Cyclophosphamide/Vincrisitine/Procarbazine/Prednisolone, FFP: Freedom from Progression

Introduction

Treatment of early stage (stage I-II) Hodgkin's lymphoma (HL) with combined modality therapy (CMT), consisting of chemotherapy and radiotherapy, is a highly effective curative treatment [1]. CMT yields long-term overall survival (OS) exceeding 90% [2]. However, patients are often young and can experience late treatment-related toxicities including secondary tumours, cardiac events, and lung disease. More early stage patients die from late treatment related toxicities than HL, suggesting an element of overtreatment [2]. As an alternative to CMT, guidelines now include chemotherapy alone as an option in early stage HL [3]. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) is now vital in HL for both staging and assessing treatment response. A positive FDG PET scan post-treatment strongly predicts relapse whilst a negative FDG PET result strongly predicts progression-free survival (PFS) [4]. Furthermore an interim FDG PET after 1-3 cycles of chemotherapy also predicts final treatment response and PFS [2]. Currently trials are evaluating risk-adapted therapy whereby radiotherapy is omitted in early stage disease when an interim FDG PET scan is negative.

Our centre previously adopted a risk-adapted stratification based on post-chemotherapy imaging in early stage HL. When a post-chemotherapy FDG PET scan was negative radiotherapy was omitted but administered if CR was not achieved on FDG PET imaging. We aimed to retrospectively determine OS and relapse free survival (RFS) in this cohort.

Materials and Methods

Hospital records were used (pharmacy records, the regional cancer database, histology records and clinical notes) to identify early stage HL patients treated at our centre from 2005-2012. In 2005 a FDG PET scanner was installed into our centre and subsequently most patients were imaged utilising this modality. Involved field radiotherapy was the radiotherapy technique utilised for all patients. Decisions regarding choice of imaging modality and type of treatment were made by the treating physician. Patients who did not have a FDG PET-post chemotherapy were excluded from analysis (n=18). Patients who did receive radiotherapy despite CR on FDG PET-post chemotherapy were also excluded (n=10).

ClinMed International Library

Citation: Rider T, Jones J, Brewin J, Horne G, Wills J, et al. (2015) The Role of Positron Emission Tomography Imaging in the Risk-Adapted Treatment of Stage I-II Hodgkin's Lymphoma - A Retrospective Analysis. Int J Blood Res Disord 2:015

Received: April 29, 2015: **Accepted:** July 06, 2015: **Published:** July 09, 2015

Whole body FDG PET-CT images were acquired using a Siemens Biograph PET- 64 slice CT with no contrast CT material 60 minutes after an injection of 400 MBq of [^{18}F]- flurodeoxyglucose (FDG). This comprised of an initial topogram (35mA, 120kVp, slice 0.6mm) followed by the conventional non-diagnostic unenhanced low dose (mean effective dose 4.8mSv) CT without contrast material (auto mA, 120kVp, rotational speed=0.5 sec/rot, pitch=0.8, slice thickness=5mm) and PET acquisition. Patients were fasted for 6 hours prior to the study or 4 hours if diabetic. Visual assessment of FDG PET scans was undertaken to identify focal or diffuse FDG uptake compared to background uptake in the mediastinal blood pool and liver [5]. Metabolic response was categorized as CR if no residual metabolically active disease was present, PR if metabolic activity was less apparent but present or PD if there were new metabolically active or more FDG avid lesions.

Several other patients were excluded including those with HIV (n=5), splenomegaly (n=3), lymphocyte predominant disease (n=2), incomplete records (n=2) and no end of treatment FGD PET assessment (n=36). Patients with B symptoms, mediastinal disease and bulky disease (defined as a nodal mass greater than 10cm in diameter or a mediastinal mass with a maximum diameter measuring at least one-third of the maximum chest wall diameter) were included. The length of follow-up was taken from the date of the initial histology report until the end of the data collection (4/2/13), the date of last clinic attendance prior discharge, or being lost to follow-up. Data was analysed using SPSS for windows (version 20, SPSS Inc, Chicago, IL), Kaplan-Meier analyses were performed to calculate OS and PFS values.

Results

In total 36 stage I-II Ann-Arbor patients were identified for analysis. 58% were female and median age at diagnosis was 38 (range 21-70). 8.4% had stage 1a disease, 2.7% had 1b, 69.4% had 2a and 19.5% had stage 2b disease. The most common sub-type of disease was nodular sclerosing (58.3%) and the remainder were classical (22.2%), mixed cellularity (13.9%), lymphocyte deplete (2.8%) and undeterminable (2.8%). Only one patient had bulky disease, they achieved CR after 6 cycles of ABVD and therefore did not receive radiotherapy.

All patients received ABVD chemotherapy except one patient who received 2 cycles of BEACOPP followed by 2 cycles of ABVD; their treatment was administered at a different centre. The mean number of cycles of chemotherapy administered was 4.5 (range 2-6). The mean duration of follow-up was 96 months and range (2-145 months). Before chemotherapy was administered 47.3% of patients had a baseline FDG PET assessment. No patient had an interim FDG PET assessment.

36 patients had FDG PET assessment post-chemotherapy, of which 35 demonstrated CR and 1 had PR. The PR patient received radiotherapy whereas none of the CR patients received radiotherapy. No patient with CR relapsed during follow-up period (n=35). However, the PR patient did relapse, making the RFS was 97.8%. The patient who relapsed was aged 69 at diagnosis and had stage 2a classical disease with lymphadenopathy in the cervical and occipital regions. They received 4 cycles of ABVD and subsequent radiotherapy to the cervical region. At 14 months a relapse occurred in the mastoid region and they were treated with further chemotherapy and radiotherapy. A further relapse occurred at 29 months in the supraclavicular region which was a different site to their original disease. They were salvaged with further chemotherapy and remained in CR after 46 months of follow-up. There were no deaths in the cohort that received chemotherapy during the follow-up period, and therefore OS was 100%.

Discussion

We demonstrated that post-chemotherapy FDG PET negative patients can achieve durable CR and RFS when radiotherapy is omitted. This finding is in agreement with another retrospective study of 47 patients with favourable stage I-II HL treated with 6 cycles of ABVD only [6]. Patients had a baseline FDG PET scan and either an interim or post-treatment FDG PET assessment. All patients were also alive at the end of the follow-up period (range from 24-95 months). Relapse free survival was also comparable to our study as only two relapses occurred (at 7 and 24 months) and both patients were successfully salvaged with chemotherapy and autologous stem cell transplant. Both studies provide evidence that OS and RFS are not compromised when radiotherapy is omitted in selected patients, which avoids the significant long-term risk of morbidity and mortality secondary to radiotherapy. However, both studies are limited by their retrospective nature. Additionally, few deaths occurred in patients who received chemotherapy, thereby limiting survival outcome data. Prospective studies can also be affected by the high survival rates of early stage HL. It can be challenging to sufficiently power trials to enable detailed comparison of two different regimens [7]. Trials are also limited by the long-term follow-up necessary to accurately quantify late treatment-related complications. Furthermore once sufficient follow-up data has been accrued, the original chemotherapy regimens or radiotherapy techniques used will have become outdated.

The approach of using chemotherapy alone to treat early stage HL is an emerging and controversial topic. Current guidelines dispute the inclusion of chemotherapy alone as a treatment option [1,3]. Prospective trials that randomised participants upfront to CMT or chemotherapy alone have produced conflicting findings. These trials did not utilise a risk-adapted strategy based on interim or post-treatment FDG PET results. Two trials have compared 6 cycles of ABVD only or CMT. The first trial included stage I-IV patients with bulky disease and B symptoms. After 8 years of follow-up OS (100%) and PFS (88%) were higher in the CMT group (P=0.002 and P=0.01 respectively) compared to the chemotherapy only arm (OS 89% and PFS 76%) [8]. By contrast the second trial, which included patients with stage I-IIIA non-bulky disease, failed to demonstrate a superior duration of CR (P=0.61), OS (P=0.61) or PFS (P=0.08) with CMT after 5 years of follow-up. For the CMT group the OS and freedom from progression (FFP) were 97% and 86% respectively compared to OS of 90% and FFP of 81% with ABVD alone [7]. However, the trial may have been underpowered to detect small differences in outcome measures. The H9-F trial randomised stage I-II patients to receive two different doses of radiotherapy or no radiotherapy after 6 cycles of EBVP [9]. Recruitment into the group that did not receive radiotherapy was stopped prematurely due to excessive adverse outcomes. Four year event free survival (70%) was significantly worse in this group (P<0.001). The HD.6 trial has the longest follow-up period of any trial and therefore provides more extensive data on treatment-related toxicities [10]. Stage IA or IIA non-bulky HL patients received 4-6 cycles of ABVD only or subtotal nodal radiotherapy. The radiotherapy group was sub-divided; those with a favourable disease received radiotherapy only and patients with unfavourable disease received radiotherapy plus 2 cycles of ABVD. After 12 years of follow-up, OS was higher in the chemotherapy-only group compared to the radiotherapy group (94% versus 87%, HR 0.50 95% CI 0.25-0.99, P=0.04), however, the former group had a worse PFS (87% versus 92%, HR 1.95 95% CI 0.54-1.33, P=0.05). In the chemotherapy-only group there were fewer deaths from secondary cancers and fewer cardiac events. Notably however, the radiotherapy technique employed is now outdated. Interestingly the chemotherapy-only group were re-scanned after 2 cycles of ABVD, and although the interim scan did not influence treatment strategy those achieving CR had higher PFS (HR 0.28 95% CI 0.10-0.83 P=0.02).

One meta-analysis has been conducted which included 5 trials using either CMT or chemotherapy alone in HL [11]. The meta-analysis concluded better disease control (HR 0.41 95% CI 0.25-0.66) and OS (HR 0.40 95% CI 0.27-0.61) was achieved with CMT. However this meta-analysis is limited by several significant factors which would have affected outcomes; one trial included stage III disease [7], only two trials used ABVD chemotherapy, and only two used current radiotherapy techniques.

Interim FDG PET scans may indicate tumour chemosensitivity more accurately than post-chemotherapy FDG PET scans [12]. A

good response earlier in treatment implies that the rate of tumour cell death is sufficient to produce a cure by the end of treatment [12]. Patients with a negative interim FDG PET may therefore benefit less from additional radiotherapy whilst being exposed to the potential long-term treatment-related toxicities. Currently interim FDG PET scans are only indicated as part of a clinical trial [3]. Three on-going trials will provide prospective data on the efficacy of risk-adapted approaches based on interim FDG PET imaging [12]. The RAPID trial enrolled 602 patients with favourable IA/IIA disease. Patients had 3 cycles of ABVD prior to FDG PET imaging. Those with a positive FDG PET had a fourth cycle of chemotherapy followed by involved field radiotherapy. Those with a negative FDG PET scan (75%) were randomised to receive no further treatment (n=211) or radiotherapy (N=209). Abstract publication of the RAPID trial data indicate that the 3-year PFS of patients who had a negative interim FDG PET result and who were given CMT was 93.8%, compared to 90.7% in those treated with chemotherapy only (risk difference -2.9%, 95% CI -10.7 to 1.4%) [13]. The lower limit of the confidence interval does, however, exceed the predefined non-inferiority margin of 7%. 3-year OS was 97% for CMT and 99.5% for chemotherapy only. However, there were more deaths in the CMT group before radiotherapy was actually administered which could favour OS in the chemotherapy-only group in the intention-to-treat analysis. For the group with a positive FDG PET scan the 3-year PFS and OS was 85.9% and 93.9% respectively.

The interim safety analysis of the EORTC/LYSA/FIL H10 trial has been published [14]. 1137 patients with stage I/II classical disease were enrolled, which included patients with unfavourable disease. Patients with favourable disease received 3 cycles of ABVD and involved-node radiotherapy irrespective of interim FDG PET findings in the standard treatment arm (n=188). In the experimental arm (n=193), patients with a negative FDG PET scan after 2 cycles of ABVD received 2 further cycles only. Patients with a positive FDG PET scan received 2 cycles of BEACOPPesc chemotherapy plus radiotherapy. A similar strategy was adopted for the unfavourable characteristic group (standard arm n=251, experimental arm n=268) but the FDG PET negative group received a total of 6 cycles of ABVD. After a median follow-up of 1.1 years, a non-inferiority analysis compared the patients in the standard arm who had a negative interim FDG PET scan and the patients with favourable and unfavourable disease in the experimental arm who had a negative interim FDG PET scan. For the group with favourable disease the PFS was 100% in the standard arm and 94.9% in the experimental arm (all had negative FDG PET scans). The estimated hazard ratio was 9.36 (79.6% CI 2.45-35.73), P=0.017, lower than the pre-defined value of 0.102 and therefore accrual into this arm was stopped. Accrual into the arm for patients with unfavourable disease was also stopped; the PFS was 97.3% and 94.7% respectively in the standard and experimental arms with negative FDG PET scans (estimated hazard ratio 2.42 80.4% CI=1.35-4.36 P=0.026 less than predefined 0.098). The interim analysis gave no reason to stop accrual into the arm with patients with a positive interim FDG PET scan (n=1950). The final analysis of mature data is awaited which may confirm or refute the interim findings of superior outcomes with CMT.

Early stage HL has a good prognosis as shown by the OS in our cohort which was 100% matching the OS in several of the studies discussed. Decreasing long-term treatment related morbidity and mortality in HL patients has therefore been the focus of recent trials, as patients at the time of diagnosis may have a long life expectancy and no co-morbid disease. Studies that omitted radiotherapy based on initial randomisation have produced conflicting results. Either interim or post-chemotherapy FDG PET may help to refine which patients need additional radiotherapy or escalation of chemotherapy and individuals who can safely have radiotherapy omitted. The role of FDG PET in achieving this aim is yet to be fully established and widely agreed upon. Our data is limited by its retrospective nature but does suggests that in routine clinical practice at a non-specialist centre, radiotherapy can be omitted in early stage HL if post-chemotherapy FDG PET is negative.

Conclusion

The approach of omitting radiotherapy in early stage HL shows initial promise but remains controversial with supporting evidence mainly derived from studies performed in the pre-FDG PET era. Full results from recently completed and on-going trials will help clarify the efficacy of risk-adapted therapy based on interim FDG PET results. This approach tailors treatment to the individual patient based on treatment response and aims to minimise long-term treatment-related toxicities without compromising OS or RFS.

References

1. Eichenauer DA, Engert A, Dreyling M; ESMO Guidelines Working Group (2011) Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22 Suppl 6: 55-58.
2. Hutchings M (2012) How does PET/CT help in selecting therapy for patients with Hodgkin lymphoma? Hematology Am Soc Hematol Educ Program 2012: 322-327.
3. Hoppe RT, Advani RH, Ai WZ, Ambinder RF, Aoun P, et al. (2012) Hodgkin lymphoma, version 2.2012 featured updates to the NCCN guidelines. J Natl Compr Canc Netw 10: 589-597.
4. Guay C, Lépine M, Verreault J, Bénard F (2003) Prognostic value of PET using 18F-FDG in Hodgkin's disease for posttreatment evaluation. J Nucl Med 44: 1225-1231.
5. Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, et al. (2007) Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 25: 571-578.
6. Hartridge-Lambert SK, Schöder H, Lim RC, Maragulia JC, Portlock CS (2013) ABVD alone and a PET scan complete remission negates the need for radiologic surveillance in early-stage, nonbulky Hodgkin lymphoma. Cancer 119: 1203-1209.
7. Straus DJ, Portlock CS, Qin J, Myers J, Zelenetz AD, et al. (2004) Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. Blood 104: 3483-3489.
8. Laskar S, Gupta T, Vimal S, Muckaden MA, Saikia TK, Pai SK, et al. (2004) Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? J Clin Oncol 22: 62-68.
9. Noordijk E, Thomas J, Ferme C, van 't Veer M, Brice P, et al. (2005) First results of the EORTC-GELA H9 randomized trials: the H9-F trial (comparing 3 radiation dose levels) and H9-U trial (comparing 3 chemotherapy schemes) in patients with favorable or unfavorable early stage Hodgkin's lymphoma (HL). American Society of Clinical Oncology 23: 6505.
10. Meyer RM, Gospodarowicz MK, Connors JM, Pearcey RG, Wells WA, et al. (2012) ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 366: 399-408.
11. Herbst C, Rehan FA, Skoetz N, Bohlius J, Brillant C, et al. (2011) Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma. Cochrane Database Syst Rev: CD007110.
12. Kasamon YL (2011) Prognostication and Risk-Adapted Therapy of Hodgkin's Lymphoma Using Positron Emission Tomography. Adv Hematol 2011: 271595.
13. Radford J, Barrington S, Counsell N, Pettengell R, Johnson P, et al. (2012) Involved Field Radiotherapy Versus No Further Treatment in Patients with Clinical Stages IA and IIA Hodgkin Lymphoma and a 'Negative' PET Scan After 3 Cycles ABVD. Results of the UK Ncri Rapid trial. Blood 120: 547.
14. André M, Reman O, Federico M, Girinski T, Brice P, Sebban C, et al. Interim Analysis of the Randomized Eortc/Lysa/Fil Intergroup H10 Trial On Early PET-Scan Driven Treatment Adaptation in Stage I/II Hodgkin Lymphoma. Blood 120: 549.