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

Tom Rider¹, John Jones², John Brewin¹, Gillian Horne¹, Jack Wills¹, Hannah Barton¹, Kevin Boyd², Timothy Corbett², Sabina Dizdarevic¹ and Timothy Chevassut¹,2*

¹Brighton and Sussex Medical School, University of Sussex, UK
²Royal 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


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]. 18F-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]. Therefore an interim FDG PET after 1-3 cycles of chemotherapy also predicts final treatment response and PFS [5]. 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).
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 $[^{18}F]$-2-Fluoro-2-deoxyglucose (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 FDG 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 (4/12/13), 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]. The Interim FDG PET scans may indicate tumour chemosensitivity more accurately than post-chemotherapy FDG PET scans [12]. A

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.

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 use 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 suggest 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