Phase II study of interim PET–CT-guided response-adapted therapy in advanced Hodgkin’s lymphoma

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Background: Combination chemotherapy ABVD (doxorubicin, bleomycin, vinblastine and dacarabazine) cures ∼70% of patients with advanced Hodgkin’s lymphoma (aHL, stages IIb, III and IV) while more toxic escalated BEACOPP (EB, combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) increases cure rates to 85%. Patients with a positive interim positron emission tomography–computerized tomography (PET–CT) scan after two cycles (PET-2) of ABVD have very poor outcomes with continued ABVD. Intensifying therapy with EB in PET-2-positive patients (‘response-adapted therapy’) may improve cure rates, whereas the negative patients can continue ABVD alone.

Patients and methods: Eligible patients with newly diagnosed aHL received two cycles of ABVD and underwent PET-2 (scored with semi-quantitative 5-point visual criteria, ‘Deauville score’). PET-2-negative patients continued four additional cycles of ABVD, whereas PET-2-positive patients received four cycles of EB. A phase II sample size of 50 was estimated keeping the lower and higher proportion of rejection of the event-free survival (EFS) as 70% and 85%, respectively.

Results: Fifty patients [median age 28 (12–60) years; male : female: 39 : 11; stages: IIb—3 (6%), III—29 (58%) and IV—18 (36%); International Prognostic Score (IPS): 0–3: 34 (68%); 4–7: 16 (32%)] were enrolled; 49 underwent PET-2. Eight (16%) were PET-2-positive, whereas 41 (84%) were negative. Forty-seven were evaluable for EFS and all 50 for overall survival (OS). The 2-year EFS was 76% (95% CI: 68–83) and OS was 88% (95% CI: 82–94). PET-2 was strongly prognostic-2-year EFS, negative versus positive: 82% versus 50%; P = 0.013.

Conclusion: PET-2 response-adapted strategy could not achieve EFS of 85% in aHL. However, escalated therapy improved outcomes in PET-2-positive patients compared with historical data.

Trial registration: CTRI/2012/06/002741 (http://www.ctri.nic.in) and NCT01304849 (http://www.clinicaltrials.gov).

Key words: Hodgkin’s lymphoma, response-adapted therapy, interim PET–CT scan, Deauville score, EB, escalated BEACOPP

introduction

The combination of doxorubicin, bleomycin, vinblastine and dacarabazine (ABVD) given for six to eight cycles is considered as standard therapy for advanced Hodgkin’s lymphoma (aHL) [1–4]. However, ABVD fails to cure 20%–30% of patients with aHL [2, 5, 6]. Cure rates of 85%–87% can be achieved with six to eight cycles of escalated BEACOPP (EB, a dose-intense combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) [7–9]. EB causes more severe toxicities, including fatalities, when compared with ABVD [7–10]. Since three-fourths of patients with aHL can be cured with ABVD alone, using EB for all patients of HL would mean over-treatment in majority [5, 11]. If we could reliably identify the subgroup of patients who are likely to fail therapy with ABVD, more intense therapy could be tailored to that group.

The International Prognostic Score (IPS) was shown to demarcate outcomes in aHL [5, 11, 12]. However, even those with the highest IPS achieve an EFS of 67% [11]. Hence, it is not feasible to use this as a tool for escalating therapy as there may be a significant risk of over treating two-thirds of patients. More recently, an interim positron emission tomography–computerized tomography (PET–CT) scan carried out after two to three cycles
of initial chemotherapy (PET-2) has been demonstrated to be superior to IPS in its prognostic ability with the PET-2-positive and -negative patients having 3-year progression-free survival (PFS) rates of 28% and 94%, respectively [13, 14]. PET-2 positivity identifies a subset of patient with a very high chance of therapy failure with standard treatment. The use of more intense therapy like EB in these patients (response-adapted therapy) may help to overcome the poor initial response and achieve a higher cure [15]. Since only a small proportion of patients are PET-2-positive, majority can continue to receive less toxic ABVD.

One of the challenges in using the PET-2 for guiding therapy is in defining the positive scan as most scans done at this time point in patients with aHL will demonstrate some activity in the lesions. The International Harmonization Project introduced a semi-quantitative, 5-point, visual interpretation criteria (‘Deauville criteria’) which have been subsequently validated [13, 16]. We report on the early results of a phase II study in which we used the interim PET scan done after two cycles of ABVD (PET-2) to guide the use of more intensive therapy. We used the visual interpretation criteria with a 5-point discrimination score to categorize the interim PET–CT scans as positive and negative [13, 17].

patients and methods

patient eligibility

 Newly diagnosed patients (12–65 years) with advanced stage HL (Ann Arbor stages III–IV) were included. Patients had to have histological diagnosis of HL with adequate bone marrow function (white blood cell count ≥ 4000/cmm, platelet count ≥100 000/cmm, unless deranged due to involvement by HL) and adequate organ function (serum creatinine ≤2mg/dL and serum bilirubin, SGOT and SGPT ≤2.5 times upper limit of normal). Patients with co-existent cardiac or pulmonary diseases or uncontrolled diabetes and hypertension were excluded. Female patients could not be pregnant and had to consent to use effective contraception during the study. All patients underwent PET–CT before treatment.

study design and treatment

This was an investigator-initiated, open label, single-center phase II study. Patients were recruited between January 2011 and October 2013. At the time of data analysis, all patients had completed the planned treatment and end-therapy evaluation.

The study was approved by the institutional review board, and all patients gave informed consent. Eligible patients started therapy with two cycles of ABVD and underwent an interim PET–CT scan (PET-2). Patients with a negative PET-2 continued four more cycles of ABVD (total six cycles of ABVD). Patients with a positive PET-2 received four cycles of EB (total 2 ABVD + 4 EB). All patients underwent end-therapy PET–CT scans. Those who had a significant positive disease (lymph node size ≥2 cm with a Deauville score of 2/4) underwent biopsy of the positive areas whenever feasible. Disease sites that could not be biopsied but were suspicious were followed up with repeat imaging after 3–6 months. They were biopsied if persistent or growing. All others with negative scans at completion of treatment were kept on clinical follow-up (every 3 months for the first 2 years and every 6 months after that). Radiation was given by a protocol to all sites of initial bulky disease, but was allowed to be omitted in those with a PET score of 1 at the end of therapy.

ABVD was delivered as per the original schedule and EB was delivered as per the doses used in the HD-9 study [1, 7]. All cycles of EB were delivered as inpatient with prophylactic antifungal and antibiotic coverage and routine use of prophylactic granulocyte colony-stimulating factor (GCSF) from day 9 (D9) of each cycle. Among those receiving ABVD, GCSF use was restricted to those who developed grade 4 neutropenia, febrile neutropenia or delay of >3 days. Patients were examined before every cycle and adverse events were graded using the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 3.0.

PET–CT scanning and interpretation

method of PET–CT scanning. PET was carried out using a GE PET–CT discovery model with 64-slice CT facility. A dose of 18F-FDG of 7.5 MBq/kg was administered intravenously. Two-dimensional acquisitions were made from vertex to mid-part of the thigh 60 min after iv administration. Patients were required to fast at least 6 h prior and avoid physical stress at least 24 h before the study. Blood sugar was kept between 150 and 200 mg/dL. Acquisition times were 16 min (8 bed positions/2 min per bed position) for the emission scans and 5 min for transmission scans. CT images were acquired immediately before the PET scan for attenuation correction and localization of PET uptake. All images were processed by the software provided by the GE discovery model (ADW) and the Xelerix unit.

Standardized uptake values were assessed using region of interest (ROI) and visual criteria, and normalized for actual body weight. ROI with a diameter corresponding to 75% of the maximal lesion activity was used as threshold to reflect the most active part of the tumor and to ensure consistent ROI drawings.

timing of the scans. Baseline PET–CT (PET-0) was done at the time of diagnosis, PET-2 was carried out 2–3 days before the next cycle of chemotherapy and the final scan was carried out at least 4 weeks after the last dose of chemotherapy.

interpretation of PET–CT scans. Interim PET images were scored according to the 5-point visual interpretation score (the ‘Deauville score’) [16]. The uptake in the involved area was visually compared with mediastinum and liver as reference organs. Score 1 was no uptake, 2 was uptake ≤mediatinum, 3 was uptake >mediastinum and ≤spleen, 4 was uptake moderately increased above liver at any site and 5 was markedly increased uptake at any site and new sites of disease. Since this was a trial with an escalation strategy with an aim of limiting exposure to toxic therapies, scores ≤3 on the PET-2 were considered as negative (patients continued 4 more cycles of ABVD) and scores 4 or 5 were considered as positive (patients changed from ABVD to 4 additional cycles of EB). PET images were interpreted by a single nuclear medicine physician with over 20-year experience. No second review was planned during the trial.

statistical analysis

The primary end point was EFS which was calculated from the start of first cycle of therapy to date of occurrence of the event. ‘Event’ was defined as relapse after previous complete remission or progression after documenting partial remission or progressive disease (a 50% increase from nadir of any previous partial remission lesions or appearance of new lesions) on computed tomography scan measurements during protocol treatment or death resulting from any cause, whichever occurred first. Historically, six to eight cycles of ABVD results in 5-year EFS of 61%–73% in advanced HL [2, 5]. The more intense regimen of EB results in 5-year EFS of 85%–87% [7]. We hypothesized that PET-2-guided therapy could improve the EFS to 85% compared with the historical EFS of 70% with ABVD. Using Fleming’s one-stage procedure (probability of type I error α = 0.05 and power = 0.8),
keeping the lower proportion of rejection (p0) as 70% and the higher proportion of rejection as 85%, the estimated sample size was 50.

The secondary end points were overall survival (OS) and toxicity of EB. EFS and OS were estimated using the Kaplan–Meier method. The impact of various prognostic factors was estimated using the log-rank test and Cox regression multivariate analysis was done. Analyses were done using the SPSS software, version 13.

results

patient characteristics
Fifty patients (Table 1) were enrolled (median age 28 years, range 12–60 years), including 39 males (78%) and 11 females (22%). Three patients (6%) had stage IIB disease, whereas 29 (58%) and 18 (36%) had stage III and IV diseases, respectively. Sixteen patients (32%) had a high-risk disease (IPS of 4–7).

treatment and outcomes
All 50 patients received initial treatment with two cycles of ABVD chemotherapy. One patient did not undergo an interim PET–CT scan. Forty-nine had interim PET–CT scans (supplementary Table S1, available at Annals of Oncology online)—of these, 8 (16%) were scored positive (score 4 or 5) and the rest (N = 41, 84%) were negative (score 1–3). Three patients defaulted after two, four and five cycles of chemotherapy (one did not undergo PET-2 and the other two were PET-2-negative) and have not undergone end-therapy evaluation of disease status (they are alive but have not come back to the treatment center for evaluation). These are excluded from EFS analysis (as their final disease status is unknown), but included in the OS analysis. End-therapy scans were positive (Deauville score ≥4, size ≥2 cm) in five patients (on biopsy, four were positive for HL and one was reactive). Three other patients had residual lesions of 1–1.5 cm with scores ≥4 in the mediastinum (not amenable for biopsy). They were kept on follow-up and showed regression of lesions on follow-up scans (3 and 6 months).

dose intensity and therapy delays
The median relative dose intensity among those who received six cycles of ABVD was 94% and among those who received four cycles of EB was 95%. The median time to complete six cycles of ABVD was 25.2 weeks (expected: 24 weeks) and for four cycles of EB was 93 days (expected: 92 days). The median time to perform the interim PET–CT scan after the cycle 2 (C2), D15 ABVD course was 14 days (range: 12–19 days), with 81% completing PET-2 by D15. C3 D1 chemotherapy was delivered at a median of 17 days (expected start is 15th day) in those with negative PET-2 (who continued ABVD) and at a median of 20 days in those with positive PET-2 (changed to EB) after C2 D15.

outcomes of PET-2-positive patients (N = 8). One of the PET-2 positive patients developed severe liver dysfunction due to involvement by progressive HL. He was considered unfit to receive EB and was taken off the protocol. Seven patients received four cycles of EB. Five (of 7) achieved complete remission at end of therapy and four remained so till last follow-up. Of the remaining three patients, one relapsed 6 months after completion of treatment and two had progressive disease in the final PET–CT scan. Thus, of the eight patients with a PET-2-positive disease, four remain event-free.

outcomes of PET-2-negative patients (N = 41). These patients were to complete four more cycles of ABVD and then undergo end-therapy evaluation scans. Thirty-nine of these had undergone end-therapy scans and were available for assessment. Thirty-four (of 39) remain in remission, whereas five have progressed.

survival analysis and prognostic factors. After a median follow-up of 24.7 months (range: 3.2–44 months), the median EFS and OS have not been reached. The estimated 2-year EFS (N = 47) was 75.7% (95% CI: 68.4–83.0, Figure 1A).

On univariate analysis (Table 2), interim PET-2 positivity was the only factor which was predictive of EFS. PET-2-positive patients had an inferior EFS when compared with PET-2-negative patients despite escalation of therapy (2-year EFS 82% versus 50%; P = 0.013, Figure 1B).

Of the 50 patients enrolled in the study, 4 have died—3 due to progressive disease and 1 due to unknown cause. The estimated 2-year OS (N = 50) was 87.7% (95% CI: 81.6–93.8).

safety and tolerability of escalated BEACOPP
Seven patients received EB chemotherapy (28 cycles) and acute grade 3/4 toxicity details are presented. There were no non-hematological grade 3/4 toxicities due to EB. Grade 3/4 neutropenia occurred in 24/28 (85%) of the cycles and febrile neutropenic episodes occurred in 14/28 (50%) of the cycles. Two patients required red cell transfusions for grade IV anemia and one patient required platelet transfusion for grade IV thrombocytopenia. There were no deaths due to toxicity from treatment.

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Table 1. Baseline characteristics of the patients (N = 50)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Median</td>
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<td></td>
</tr>
<tr>
<td>Range</td>
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<td></td>
</tr>
<tr>
<td>Males</td>
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<td>78</td>
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<td>ECOG performance status</td>
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<td>0–1</td>
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<td>94</td>
</tr>
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IPS: International Prognostic Score.
This is one of the first prospective studies to report on the outcomes of PET-2-guided dose-escalation strategy in aHL. With the use of this strategy, intensive EB use was restricted to 16% of the total patients while majority were spared excess toxicity. The entire cohort realized 2-year EFS of 75.7% (95% CI: 68.4–83.0). It is clear that this strategy will not be able to realize 5-year EFS of 85% which was the primary end point. Despite this, this trial yielded important messages. The strong prognostic ability of the interim PET-2 scan was conclusively proved with an inferior outcome in the PET-2-positive patients despite escalation of therapy. This trial also raises questions about the actual negative predictive value of the PET-2 scan as we saw 5/39 (13%) patients suffering progression despite having a negative scan. This is one of the first reported trials to prospectively utilize the Deauville score to guide therapy and showed the feasibility of carrying out response-guided treatment strategy in aHL.

Eight of 50 patients had positive scans (17%) in our study, an interim PET-positivity rate which is similar to other reports [13]. After receiving more intensive EB, four of the eight remained event-free (2-year EFS of 50%). Compared with the earlier data of EFS of 28% in the PET-2-positive cohorts when treated with continued ABVD, this represents a definite improvement [13, 18]. Retrospective studies have reported a 2-year PFS rate of 65% following intensification of treatment in PET-2-positive patients [15]. A prospective trial involving pediatric HL and more recently published abstracts of adult aHL trials have also demonstrated the feasibility of salvaging some of the poor responders with more intense therapy [19–22]. Thus, response-guided therapy is a reasonable strategy which improves outcomes in a very poor subset of aHL.

However, despite the success achieved with salvaging half the PET-2-positive patients, the overall cohort did not achieve the target EFS of 85%. Based on retrospective data, the expected EFS in PET-2-negative patients treated with ABVD is 94% [13]. However, in our study, 5 (of 39) with negative PET-2 progressed (2-year EFS of 81%). Preliminary data from other prospective studies enrolling similar patients and with comparable rates of PET-2 positivity (16%–20%) show 2-year PFS results of 85% in PET-2-negative patients which is closer to our results [20–22]. Though this trial was not undertaken to specifically address this question and the fact that small sample size may limit interpretation, a review of the negative predictive value of the PET-2 scan (scores 1–3) should be considered. Another limitation of our study was that we did not carry out independent review of scans as part of the trial (3/5 relapsing patients with PET-2-negative scans had a score of 3) and is now planned to be done retrospectively. Though there was a median of 2 days delay in starting

**Table 2.** Univariate analysis of factors affecting the event-free survival (N = 47)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>2-year EFS%</th>
<th>P-value</th>
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</tr>
<tr>
<td>Absent</td>
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<td>68</td>
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</tr>
<tr>
<td>Present</td>
<td>32</td>
<td>79</td>
<td></td>
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<tr>
<td>Bulky disease</td>
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<td></td>
</tr>
<tr>
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<td>36</td>
<td>68</td>
<td>0.08</td>
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<tr>
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</tr>
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<td>31</td>
<td>83</td>
<td>0.112</td>
</tr>
<tr>
<td>4–7</td>
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</tr>
<tr>
<td>Interim PET</td>
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</tr>
<tr>
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<td>39</td>
<td>81</td>
<td>0.019</td>
</tr>
<tr>
<td>Positive</td>
<td>8</td>
<td>50</td>
<td></td>
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</table>

PET: positron emission tomography; EFS: event-free survival.

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**Figure 1.** (A) Kaplan–Meier survival curve showing the event-free survival (EFS, dotted line) and overall survival (OS, bold line) of the entire cohort. (B) EFS depending on the outcome of interim PET–CT scan carried out after two cycles of ABVD chemotherapy (bold line: PET-2-negative; dotted line: PET-2-positive). PET: positron emission tomography; CT: computerized tomography; ABVD: doxorubicin, bleomycin, vinblastine and dacarbazine.
the C3 D1 after the interim PET-2 scan, majority of the patients were able to maintain acceptable dose intensity during the protocol.

Despite limitations, this study underscores the utility of interim PET–CT scans in the management of aHL, with clear prognostic ability and possibly as a therapy-altering tool. Limited data are available on the treatment of HL from India and most centers use ABVD with results similar to the West [5]. PET-guided dose-escalation may be a feasible approach which may improve outcomes. This is important information in the Indian context as there is limited literature pertaining to the use of PET–CT scans in this country, and the currently available data suggest significant concerns about interpretation [23].

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**Disclosure**

The authors have declared no conflicts of interests.

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