Discordant PET Findings and a High Relapse Rate Characterize Hispanics With Hodgkin’s Lymphoma Treated With ABVD

SUMIT GAUR¹, ALEXANDER PHILOPOVSKIY¹, UMEANAETO ONYEDIKA¹, ANNA M. EIRING², ALOK K. DWIVEDI¹ and ATTILIO ORAZI⁴

¹Department of Internal Medicine, Texas Tech University Health Science Center- El Paso, Paul L. Foster School of Medicine, El Paso, TX, U.S.A.;
²Center of Emphasis in Cancer, Department of Molecular and Translational Medicine, Texas Tech University Health Science Center, El Paso, TX, U.S.A.;
³Division of Biostatistics and Epidemiology, Department of Molecular and Translational Medicine, Texas Tech University Health Science Center, El Paso, TX, U.S.A.;
⁴Department of Pathology, Texas Tech University Health Science Center, El Paso, TX, U.S.A.

Abstract. Background: Population-based studies on Hodgkin’s lymphoma (HL) have shown reduced survival in Hispanics and non-Hispanic Blacks compared with non-Hispanic Whites. To better understand the factors contributing to this outcome discrepancy, we retrospectively reviewed the charts of patients with HL diagnosed and treated at a single institution located along the Texas–Mexico border. Patients and Methods: We performed a retrospective chart review of all patients with HL treated at our institution over an 8-year period (2011-2018). The International Prognostic Score was calculated for all patients and results of positron-emission tomography (PET) scans (interim and end of treatment) were also recorded. Variables analyzed included tumor-related findings (stage, subtype of HL), treatment history (chemotherapy regimen including number of cycles, dose intensity and radiation treatments) and neutrophil to lymphocyte ratio. Quantitative variables were described using median, interquartile range, minimum and maximum observations. Categorical variables were described using frequency and proportions. Kaplan–Meier curves were used to show relapse-free survival. Results: A total of 24 patients were treated in the time frame, of whom 23 were Hispanic. All were treated with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) or an ABVD-like regimen. Dose intensity for chemotherapy exceeded 90%. After a median follow-up of 43 months, the relapse rate was 45.8%. Positive and negative predictive values for interim PET (0% and 50%) and end of therapy PET (80% and 58%) were suboptimal to allow for a PET-adapted therapeutic approach. Conclusion: Hispanics have a high relapse rate following ABVD which is not fully explained by universally accepted prognostic factors. Performance of PET scan in predicting outcomes of HL needs to be further studied and optimized before adopting a PET-adapted treatment paradigm for underserved Hispanic populations.

This article is freely accessible online.

Correspondence to: Sumit Gaur, MD, Department of Internal Medicine, Texas Tech University Health Science Center- El Paso, Paul L. Foster School of Medicine, 4800 Alberta Ave, El Paso, TX 79905. U.S.A. Tel: +1 9152155200, Fax: +1 9152158640, e-mail: sumit.gaur@ttuhsc.edu

Key Words: Hodgkin’s lymphoma, Hispanic, ABVD, disparity, PET.

©2021 International Institute of Anticancer Research
www.iiar-anticancer.org
In this context, the results of a positron-emission tomography (PET) scan obtained after a few cycles of therapy have shown promising results towards tailoring therapy based on risk. For example, patients who are treated upfront with ABVD and do not have a complete metabolic response on PET after a few cycles can be escalated to BEACOPP; patients who are treated upfront with BEACOPP and have a complete metabolic response after a few cycles may be de-escalated to ABVD (3, 4). For early-stage disease, interim PET has the potential to identify those patients who can safely avoid radiotherapy. This ‘PET-adapted approach’ is recommended by the National Comprehensive Cancer Network (NCCN) for the management of advanced HL (5).

Population-based studies have shown disparities in outcomes of HL, with minorities having lower 5-, 10- and 15-year survival rates as compared to Caucasians (6). There are many potential causes of these disparities, including lack of health insurance, presenting at a later stage with more advanced disease, pre-existing comorbidities and possibly biological differences, such as inherited genomic mutations. El Paso County in West Texas is predominantly Hispanic/Latino (83.1%). Data from 2011 to 2017 obtained from the Texas Cancer Registry confirm a higher age-adjusted mortality rate for HL in El Paso [0.69 (5% confidence interval=0.4-0.8)/100,000/year] compared to rest of Texas [0.3 (95% confidence interval=0.3-0.4)/100,000/year] (7). In the present study, we performed a retrospective chart review to better understand the various factors contributing to this disparity.

Patients and Methods

This single-institution retrospective chart review was performed at Texas Tech University Health Science Center El Paso, in association with University Medical Center, El Paso, which provides safety net oncology services to all patients in El Paso County, irrespective of insurance status.

This study was approved by the Institutional Review Board of Texas Tech University Health Science Center, El Paso (E20077) and appropriate Ethics Committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study received a waiver from the Institutional Review Board for obtaining informed consent. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

All patients who were treated for HL from 2011 to 2018 were identified using the university’s tumor registry. Chart review was performed to extract demographic data (age, sex, ethnicity, insurance status), tumor-related findings (stage, subtype of HL), and treatment history (chemotherapy regimen including number of cycles, dose intensity and radiation treatments). Relative dose intensity (RDI) of chemotherapy was defined as the fraction of drug dose administered relative to the standard dose. Treatment delays and their causes were recorded. The International Prognostic Score (IPS) was recorded for all patients (8). The neutrophil to lymphocyte ratio (NLR) was calculated based on available laboratory results closest to the date of pathological diagnosis. Patients with early-stage disease (stage I and II by Ann Arbor staging criteria) were divided into favorable and unfavorable subgroups based on NCCN criteria (bulky mediastinal disease or >10 cm mass, erythrocyte sedimentation rate >50 mm/h, three or more sites of involvement, presence of B symptoms). Lugano criteria were used to record PET results, with a Deuville score of 1, 2 and 3 considered as complete metabolic response (9). Date of relapse and date of death were recorded. For patients who experienced relapse, further lines of therapy were recorded.

Statistical analyses. Quantitative variables were described using median, interquartile range, minimum and maximum observations. Categorical variables were described using frequency and proportions. Kaplan–Meier curves were used to show relapse-free survival. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PET scan in predicting relapses were calculated. All analyses were carried out using STATA v.15. (Statacorp LLC, College Station, TX, USA).

Results

Table 1 summarizes the demographic and tumor related findings. A total of 24 patients with HL were treated in the given time frame, of whom 23 (95.8%) were Hispanic. Forty-five percent of the patients lacked health insurance and were dependent on charity care. After a median follow-up of 43 months, 11 patients (45.8%) had experienced relapsed (Figure 1).

Among the 15 patients with advanced stage disease (stage III and stage IV), the median IPS was 4 (range=1-6). Fourteen patients (93.3%) were treated with 6 cycles of ABVD, while one received rituximab-doxorubicin, vinblastine, dacarbazine for Epstein–Barr virus associated CD20+ mixed cellularity HL. The relapse rate in advanced-stage disease was 53.3%.

Among the nine patients with early-stage disease (stage 1 and 2), seven met one or more NCCN criteria for ‘unfavorable’ disease (three had bulky disease, six had B symptoms, and three had erythrocyte sedimentation rate more than 50 mm/h). Three were treated with four cycles of ABVD and radiotherapy, three received 6 cycles of ABVD and radiotherapy, two received 6 cycles of ABVD alone and one received 4 cycles of ABVD alone. The relapse rate in early-stage disease was 33.3%.

The RDI (ratio of chemotherapy dose received by the patient relative to the planned dose, expressed as a percentage) for each chemotherapy drug in ABVD for the entire cohort was as follows: Doxorubicin: 98.8%, bleomycin: 82.1%, vinblastine: 97.9%, and dacarbazine: 100%. Nine patients (37.5%) completed all planned therapy with no delays during treatment. For the remaining 15 patients, the average delay in completing therapy was 16 days (median 11 days, range=3-56 days).
Of the 11 patients who experienced relapse, six successfully underwent autologous stem cell transplantation (ASCT) following salvage therapy. Two out of the six received ifosfamide/carboplatin/etoposide followed by ASCT, while the remaining four required additional cycles with dexamethasone/cytarabine/cisplatin (n=2), brentuximab (n=4), cisplatin-gemcitabine (n=1), checkpoint inhibitors (n=2) while awaiting transplant.

Of the five patients who did not receive ASCT, two have been treated with 4 cycles of ifosfamide/carboplatin/etoposide followed by radiotherapy and have been on brentuximab; two are receiving checkpoint inhibitors; and one is being treated with gemcitabine, vinorelbine, bendamustine. There has been only one mortality in the cohort. This occurred in a patient with relapsed disease who died due to transplant-related complications.

Twelve patients had an interim PET assessment during therapy (eight after 2 cycles, two after 3 cycles and two after 4 cycles). Ten were found to have a complete metabolic response, of which five experienced relapse. Two were considered to have residual active lymphoma, neither of whom has experienced relapsed.

Seventeen patients had end of treatment PET-computed tomography (68%). There was a complete metabolic response in 12, with relapse in seven. Five were considered to have less than complete metabolic response, of whom four have experienced relapse. The sensitivity, specificity, PPV and NPV of interim and end of treatment PET are shown in Table II.

Table I. Patient characteristics (N=24).

<table>
<thead>
<tr>
<th>Value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median (range) 31.5 (19-68)</td>
</tr>
<tr>
<td>Gender, n (%) Male</td>
<td>11 (45.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (54.3%)</td>
</tr>
<tr>
<td>Ethnicity, n (%) Hispanic</td>
<td>23 (95.8%)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Subtype, n (%) Nodular sclerosis</td>
<td>12 (50%)</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td>Lymphocyte rich</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Lymphocyte depleted</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>7 (29.1%)</td>
</tr>
<tr>
<td>Advanced stage, n (%) III</td>
<td>5 (20.8%)</td>
</tr>
<tr>
<td>IV</td>
<td>10 (41.7%)</td>
</tr>
<tr>
<td>Early stage, n (%) Favorable</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>7 (29.2%)</td>
</tr>
<tr>
<td>IPS score, n (%) 0-3</td>
<td>13 (54.16%)</td>
</tr>
<tr>
<td>≥4</td>
<td>11 (45.83%)</td>
</tr>
</tbody>
</table>

IPS: International Prognostic Score.

Table II. Performance of positron-emission tomography (PET) in predicting outcomes.

<table>
<thead>
<tr>
<th>Interim PET</th>
<th>End of treatment PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>0.00% (0.00-52.18%)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>71.43% (29.04-96.33%)</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>0</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
<td>50% (38.5-61.5%)</td>
</tr>
<tr>
<td>Accuracy (95% CI)</td>
<td>41.67% (15.17-72.33%)</td>
</tr>
</tbody>
</table>

CI: Confidence interval; NPV: negative predictive value. PPV: positive predictive value.

Of the 11 patients who experienced relapse, six successfully underwent autologous stem cell transplantation (ASCT) following salvage therapy. Two out of the six received ifosfamide/carboplatin/etoposide followed by ASCT, while the remaining four required additional cycles with dexamethasone/cytarabine/cisplatin (n=2), brentuximab (n=4), cisplatin-gemcitabine (n=1), checkpoint inhibitors (n=2) while awaiting transplant.

Of the five patients who did not receive ASCT, two have been treated with 4 cycles of ifosfamide/carboplatin/etoposide followed by radiotherapy and have been on brentuximab; two are receiving checkpoint inhibitors; and one is being treated with gemcitabine, vinorelbine, bendamustine. There has been only one mortality in the cohort. This occurred in a patient with relapsed disease who died due to transplant-related complications.

Twelve patients had an interim PET assessment during therapy (eight after 2 cycles, two after 3 cycles and two after 4 cycles). Ten were found to have a complete metabolic response, of which five experienced relapse. Two were considered to have residual active lymphoma, neither of whom has experienced relapsed.

Seventeen patients had end of treatment PET-computed tomography (68%). There was a complete metabolic response in 12, with relapse in seven. Five were considered to have less than complete metabolic response, of whom four have experienced relapse. The sensitivity, specificity, PPV and NPV of interim and end of treatment PET are shown in Table II.

Discussion

We found a high relapse rate of 45.8% in our predominantly Hispanic patients with HL. Previous studies in multiple malignancies have identified stage at diagnosis to have the largest effect on racial/ethnic survival disparities. Most of our patients presented with advanced-stage disease (stage III and IV; 62.5%) or with unfavorable risk early-stage disease...
(29.1%). However, advanced stage at presentation does not fully explain the high relapse rate in the present study because multiple recent phase III trials in advanced stage HL have reported a relapse-free survival rate in the range of 73-76% with ABVD (1,2).

Originally described in 1998, the IPS is the most widely used prognostication tool for advanced stage HL. In addition to stage, it includes the following variables: Age, sex, albumin level, hemoglobin level, total white blood cell count, and lymphocyte count (or % of total white blood cell count), with a higher total score correlating with higher risk of relapse. In the original report, freedom from progression (FFP) at 5 years for patients who had an IPS score 0-3 was 70±2%. For patients with a score of 4 or higher, FFP at 5 years was 47±2% (8). The outcomes of HL treated with ABVD have improved over time, chiefly due to better supportive care. In more contemporary data sets, IPS retains its prognostic value; however, FFP at 5 years had increased to 81±2% for risk group 0-3 and 69±4% for risk group ≥4 (10, 11). Remarkably, the percentage of patients who presented with IPS 0-3 (81%) and ≥4 (19%) remained stable in the two data sets (8, 10).

In contrast, 45.83% of patients in our cohort presented with score of ≥4. This suggests that there may be inherent difference in biology of HL in our cohort, with a much higher proportion presenting with a high risk IPS. However, this also only partially explains the high relapse rate when taking into account more contemporary data on relapse risk associated with IPS.

PET has become the preferred imaging modality for HL. Early studies suggested tumors which become PET-negative after first 2-3 cycles of ABVD have an excellent prognosis, with a relapse rate of less than 10% (12, 13). Gallamini et al. showed that interim PET scan results had more prognostic relevance than IPS in predicting relapse (12). More recent metaanalysis suggests interim PET has a sensitivity and specificity in the range of 70.8-81% and 89.9-97%, respectively (14, 15). These results formed the basis of risk-adapted treatment of HL, in which therapy can either be safely de-escalated in good-risk patients or escalated in poor-risk patients without compromising outcomes (14, 16). Similarly, studies have confirmed the value of end-of-therapy PET scan in assessing response and the International Working Group has recommended PET scan for response assessment since 2007 (17). A recent meta-analysis showed the pooled sensitivity and specificity of PET in the assessment of residual disease at the end of treatment to be 84% and 90%, with a PPV of 90-92% and NPV of 94-100% (18, 19).

In stark contrast, in our patient population, interim PET lacked sensitivity and specificity for making meaningful clinical decisions (PPV: 0% and NPV: 50%). Only one patient had a change in treatment based on interim PET (omission of bleomycin after 2 cycles of ABVD based on negative interim PET). This patient experienced relapse 3 months after completing therapy. End of treatment PET seemed to perform marginally better, with a PPV of 80%, but a low NPV of only 58%.

The cause of this discrepancy is unclear. Specific guidelines regarding technique, timing and interpretation of PET scans are widely available, however, it is unclear as to what extent these are followed in medically underserved areas (20). Hispanics tend to have higher prevalence of metabolic syndrome and glucose intolerance. Studies have documented that many PET imaging centers do not adequately communicate pre imaging instructions to optimize scans for patients with hyperglycemia (21). Irrespective of the cause, the above data suggest that PET-adapted therapy is unlikely to be beneficial for most of our patients.

Dose intensity of chemotherapy has been shown to affect outcomes in HL when treated with mechlorethamine, vincristine, procarbazine and prednisone regimen (22). Studies in Europe and the US have shown that delivery of ABVD is suboptimal (≥85% RDI) in 18-22% of patients, however, its impact on outcomes is not clear (23). A single-institution study found no difference in outcomes when comparing three cohorts of ABVD-treated patients with RDI: >90%, 80-89% and <80%; the mean RDI of the entire group was 83% (24). Indirect evidence of the importance of maintaining RDI and schedule of ABVD comes when looking at the data from the German Hodgkin Disease 9 (HD 9) trial (25) and the European Organization for Research and Treatment of Cancer (EORTC) 20012 trial (26). In the HD 9 trial, 8 cycles of escalated dose BEACOPP was superior to 8 cycles of hybrid regimen of cyclophosphamide vincristine procarbazine prednisone (COPP)/ABVD (a regimen equivalent to 8 cycles of ABVD). However, the median duration between the first and last day of drug administration for COPP/ABVD was 46.3 weeks (30 weeks planned) and 24.7 weeks for escalated dose BEACOPP (23 weeks planned). In contrast, in the EORTC 20012 trial, the RDI for ABVD exceeded 90% and there was no difference in the primary outcome of event-free survival when compared to BEACOPP.

In our patient cohort, the RDI of ABVD exceeded 90% and the median delay in completing the planned therapy was only 5.5 days (range=0-56 days). As such, this does not adequately explain the high rate of relapse.

The NLR has been reported to influence prognosis in multiple malignancies including lymphomas. For HL, studies have shown the adverse prognostic impact of NLR >6 (27-29). The median NLR for our patient cohort was 4.5 (range=0.52-16.6), similar to that reported in these studies, and as such is unlikely to explain the high relapse rate.

Previous studies have also shown sub-optimal outcomes with ABVD in Hispanics with HL. Ofori-Ntow et al. reported a complete response rate of 52% in Hispanic as compared to
75% in Whites (30). Jaime-Perez et al. recently reported that 43% of their Mexican patients had disease which was primarily refractory to ABVD-like regimens (31). In another single-institution study from South Texas, Martinez et al. reported similar overall survival but a higher relapse rate in Hispanics as compared to Whites (32). Our study adds to the growing data suggesting that Hispanic patients have suboptimal outcomes with ABVD. Minorities face barriers to medical care and in our study only 45% of the patients who experienced relapse were able to receive ASCT. As such, it becomes all the more important to improve the efficacy of first-line therapy and prevent relapses.

We are unable to explain the high relapse rate based on clinical prognostic features such as stage, IPS, or NLR. Dose intensity and dose density of chemotherapy were maintained at levels higher than those reported and also do not explain the high relapse rate.

Inherited gene polymorphisms affecting chemotherapy metabolism have been shown to affect outcomes in HL and these should be studied further in Hispanic populations (33). Our study also shows the challenges of adapting a PET-based approach in the management of underserved minority patients. Although intensive regimens such as escalated-dose BEACOPP might seem attractive, the poor performance of PET scan in predicting outcomes makes it impossible to safely escalate or de-escalate therapy based on PET findings.

A chief limitation of our study is that it was a single-institution study with a small sample size. Our Hispanic population was predominantly of Mexican American heritage and the findings of our study may not be applicable to Hispanics of other backgrounds.

Conclusion

Hispanics with HL have a suboptimal response to ABVD which is not fully explained by traditional HL prognostic factors. Our study also suggests physicians treating HL in Hispanic patients should use caution in adopting a PET-adapted strategy.

Conflicts of Interest

All Authors declare no conflicts of interest with regards to preparation and content of this article.

Authors’ Contributions

Sumit Gaur: Conceived the study, obtained IRB approval, abstracted data, prepared the article. Alexander Philipovsky: Contributed to the review of the article and abstraction of data. Umeanaeto Onyedika: Assisted with IRB approval, abstraction of data and review of the article. Anna M Eiring: Reviewed the article for scientific validity. Alok K Dwivedi: Statistical analysis, review of the article. Attilio Orazi: Review of the article for scientific validity.

References


20 ACR-SPR practice parameters for performing FDG-PET/CT in Oncology 2016. Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/fdg-pet-ct.pdf [Last accessed on March 1st, 2021]


Received April 3, 2021
Revised May 23, 2021
Accepted May 25, 2021