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Survival of pediatric Hodgkin lymphoma patients treated with doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) versus Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) at a single institution

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Abstract

Background: ABVD, the standard-of-care in adult Hodgkin lymphoma (HL), has not been directly compared to ABVE-PC, a pediatric regimen designed to reduce late-effects. We aimed to compare the effectiveness and associated toxicities of these two regimens used in the same institution. Methods: This retrospective cohort study evaluated a total of 224 patients diagnosed with HL between 1999 and 2018 at Children's Hospital Los Angeles (CHLA), of which 93 patients were eligible having received ABVD (n=46) or ABVE-PC (n=47) chemotherapy as their initial treatment. Descriptive analyses were performed using the Student's t-test or Fisher's exact test. Survival analysis used the Kaplan-Meier method. Events included: death, relapse, secondary malignancy, need for radiation therapy, pulmonary toxicity and cardiomyopathy determined by shortening fraction <29%. Analyses followed an intention-to-treat principle. Results: There was no difference in baseline characteristics between the patients receiving ABVE-PC or ABVD in regard for stage, risk group or prognostic variables, such as the presence or absence of "B" symptoms, bulky disease, and extra-nodal involvement. A greater proportion of patients treated with ABVE-PC received consolidating external beam radiation treatment (XRT) either by randomization or by response compared to ABVD (59.6% vs 32.6% respectively, p=0.01). While not statistically significant, response to therapy, assessed by PET/CT where available, mirrored the need for radiation (rapid response 58.3% vs 90.0%, n=34, p=0.11). There was no difference in event-free survival (p=0.63) or overall survival (p=0.37) with a median follow up length of 3.9 years. Conclusion: ABVD and ABVE-PC achieved similar survival outcomes in our single-institution cohort

Introduction

Hodgkin Lymphoma (HL) in children is treated via a number of separate protocols in the low, intermediate and high risk stratums.[1,2] In adults with HL however, ABVD has been considered the de-facto standard of care for several decades due to its effectiveness and excellent toxicity profile.[3,4] Late effects including cardiotoxicity and reduced fertility remain a concern although overall the late effects profile is favorable.[5–7]

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There is also evidence that radiotherapy can be eliminated in the low risk stratum, which is an attractive approach to reduce risk of organ toxicities and secondary malignancies.[8]

In the pediatric patient population, ABVE-PC, a dose-dense regimen has been more commonly used, especially in trials conducted by the Children's Oncology Group (COG). [1,2,9] ABVE-PC therapy is often risk-adapted and based on interim disease response.[9,10] Given the ability of children to tolerate more short-term toxicities, ABVE-PC is able to reduce exposure to anthracyclines and alkylators.[9] The COG study AHOD0031 has also shown that external beam radiation treatment (XRT) can be safely eliminated in patients with interim rapid early response .[9]

An abstract presented findings comparing AYA patients in two different clinical trials, and the results suggest that AYA patients do worse on adult protocols (ABVD vs Stanford V) when compared to pediatric protocol (ABVE-PC), with worse failure-free survival (FFS) and overall survival (OS).[11] We conducted a study to directly compare the efficacy and toxicity of ABVD to ABVE-PC for patients with HL within different disease risk strata. We hypothesized that ABVE-PC has a similar outcome as measured by EFS and OS when compared to ABVD in pediatric patients with newly diagnosed HL at our institution.

Methods

This retrospective cohort study evaluated pediatrics patients diagnosed with HL, ages 4-20 years old at diagnosis, between 1999 and 2018 at Children's Hospital Los Angeles (CHLA). Patients were identified by reviewing an already-existing database of patients maintained for the purposes of providing direct patient care. All patients who received ABVD and/or ABVE-PC as initial treatment for newly diagnosed HL were included. Patients were excluded due to either receiving a different therapy (*e.g.* bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone {BEACOPP}), incomplete therapy, receiving therapy at an outside institution of CHLA with incomplete data including pathology reports, treatment documentation and disease response evaluations.

Demographic information collected included: age at diagnosis as well as self-reported gender, race, and ethnicity. Prognostic variables abstracted from the medical record included Ann Arbor staging, presence of B-symptoms (unexplained weight loss $> 10\%$ in the preceding 6 months, unexplained recurrent fever [?] 38°C in the preceding month or recurrent drenching sweats in the preceding month), presence of splenic involvement, presence of extra-nodal disease, erythrocyte sedimentation rate at diagnosis, peripheral blood leukocyte count at diagnosis, and hemoglobin concentration at diagnosis. All chemotherapy regimens, including changes and deviations, were recorded. Results of positron emission tomography/computed tomography (PET/CT) were recorded where available. Total anthracycline doses were recorded in doxorubicin-equivalent units and reported as mg/m^2. Echocardiogram and pulmonary function testing results were recorded where available. OS was defined as the time from diagnosis to death of any cause. EFS was defined as the time from diagnosis to death, relapse/progression of disease, or diagnosis of a secondary malignancy.

Descriptive analyses were performed using the Student's t-test or Fisher's exact test for continuous or dichotomous variables, respectively. Survival analysis was performed using the Kaplan-Meier life table method. All analyses followed an intention-to-treat principle, guided by the initial therapy chosen. Late effects were analyzed and including secondary malignancy, pulmonary toxicity and cardiomyopathy determined by shortening fraction $<29\%$. We assessed treatment response from the available radiology reports, which included CT and PET/CT. Disease response was assessed by change in maximum SUV, change in the size of lymph nodes, and, if available, the Deauville score. All analyses were carried out on the R Project for Statistical Computing version 3.

All study protocols were carried out under supervision of the IRB and in compliance with the Declaration of Helsinki.

Results

224 patients with HL were screened for inclusion. Of the total charts examined 93 patients were found to be eligible; 46 patients had received ABVD and 47 patients had received ABVE-PC chemotherapy as initial

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chemotherapy. 129 patients were not included due to either receiving either a different therapy or a variation of the two therapies in question, and 2 patients were excluded due to having received initial therapy at a different institution. There were no significant differences in the two groups regarding gender, ethnicity, and race (Table 1). Of note, the ABVE-PC group contained statistically significantly older patients on average compared to the ABVD group (14.5 vs 12.7 years, p =0.03).

Known prognostic factors are summarized in Table 2. As risk classification has changed multiple times during the time period examined, patients were stratified retrospectively and uniformly into comparable risk groups utilizing the criteria employed by the COG AHOD0031 study.[9] There were no statistically significant differences found in risk stratification (Table 2,p =0.56). There were also no differences in splenic involvement, extra-nodal extension, erythrocyte sedimentation rate, leukocyte count, or hemoglobin concentration.

Patients were followed for a median of 3.9 years from diagnosis (range 0.3-18.1 years, interquartile range 1.5-5.8 years). There was no difference found in EFS and OS between patients who received ABVE-PC and those who received ABVD (Figures 1A and 1B, p =0.46 and$p$ =0.37, respectively). There was no difference in the proportion of patients requiring more than four cycles of chemotherapy or requiring a chemotherapy regimen change (Table 3). Notably, more patients in the ABVE-PC group received external beam radiation when compared to the ABVD group in intention-to-treat analysis (59.6% vs 32.6%, Table 3,p =0.01), although 6 patients achieved complete response but were randomized to receive radiation on the AHOD0031 study. When the 6 patients were analyzed as not having radiation, the difference was not statistically significant (46.8% vs 32.6%, Table 3, p =0.21). Response by PET-CT was only available for a subset of the cohort (n =34). 90% of patients receiving ABVD (n =9 of 10 total) and 58.3% of patients receiving ABVE-PC (n =14 of 24 total) had rapidly-responsive lesions on PET-CT following 2 cycles of therapy (*i.e.,* Deauville score of 1, 2, or 3) (p =0.11).

Late effects are summarized in Table 4; statistics are not available due to extremely low event rates. There were no apparent differences seen in reduced cardiac shortening fractions (SF, reduced SF defined as <29%), reduced diffusing capacity of the lung for carbon monoxide (DLCO), second malignancies or evidence of early gonadal dysfunction (as measured by follicle stimulating hormone above gender-defined norms).

Discussion

In this study, we aimed to compare two chemotherapy regimens commonly utilized at our institution for pediatric HL in regard to efficacy and toxicity. We found that there was no significant difference in EFS (p=0.46) or OS (p=0.37), with a median follow up length of 3.9 years. Our results corroborate prior published literature concerning the high overall success rate of both medication regimens and allow for direct comparison between the two regimens.[8,9]

Since treatment for HL is uniformly effective, the main challenge in developing pediatric clinical trials is to develop strategies to maintain OS while avoiding or reducing long-term morbidity. ABVE-PC, a pediatric regimen specifically designed to reduce late-effects in comparison to regimens developed in adult populations, was examined in the Children's Oncology Group AHOD0031 trial in an effort to eliminate radiation for a subset of patients. The 10-year follow up for the AHOD0031 trial found excellent outcomes for rapid early responders, and radiation therapy did not provide significant benefit in EFS over 10 years (RT 83.8% vs no RT 82.5%, p=0.26).[12] Since completion of the AHOD0031 trial however, several case series have shown that ABVD without radiation is feasible and associated with excellent outcomes in children with complete metabolic response on PET/CT imaging after chemotherapy.[13,14] When directly comparing the two regimens in similar populations, we found in our cohort that a greater proportion of patients treated with ABVE-PC received consolidating external beam radiation treatment (XRT) compared to ABVD in intention-to-treat analysis, but the difference was no longer statistically significant when patients randomized to radiation were instead analyzed as not having received radiation. Response by PET, where available, mirrored the need for radiation although the numbers available were limited.

Ultimately the goal of risk-adapted therapy, selective elimination of radiotherapy and overall reduction in therapeutic intensity is to reduce the risk of late effects and subsequent malignant neoplasms.[15] Numerous

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late effects such as hyper/hypothyroidism, thyroid nodules, heart disease, pulmonary fibrosis/pneumonitis, skin cancer in radiation field, chronic fatigue, perceived cognitive change, peripheral neuropathy, sexual changes, and osteoporosis have been described following therapy for pediatric HL.[16] Subsequent malignant neoplasms are also seen, as noted in for example in the long-term results of AHOD0031 where study authors found an excess absolute risk of 1.2 malignant neoplasms / 1000 person-years.[12] Reductions in therapy intensity have been shown to reduce the rate of late complications as well.[17] No apparent differences were seen in our cohort in regards to commonly-screened late effects or subsequent malignant neoplasms, although the low event rate for both regimens precluded analysis.

It is notable that most patients identified as Hispanic ethnicity, an expected finding that reflects the population our hospital serves as the primary free-standing children's hospital in Los Angeles and as part of the safety net for vulnerable populations. Several large studies using have shown that patients identifying with Hispanic ethnicity have had poorer survival with HL. Kahn et al found that Hispanic patients with pediatric HL had a higher risk of post-relapse mortality from pooled clinical trial data (including patients from the AHOD0031); however Kahn et al also found no difference in outcomes overall for Hispanic patients with pediatric HL when analyzing the Surveillance, Epidemiology, and End Results program in the United States.[18,19] Grubb et al found that Hispanic males had inferior disease specific survival.[20] Interestingly, the results of our study indicate overall excellent outcomes for Hispanic patients that reflect the general population with respect to EFS and OS are possible, although our numbers are small as a single institution.

There are several limitations to our study. Primarily, as this was not a clinical trial and chemotherapy regimens were chosen individually, subtle selection biases may have been introduced along with variations in number of chemotherapy courses and decisions regarding the use of radiotherapy. Second, despite collecting all the HL patients at one of the largest children's hospitals in the nation over nearly two decades, the numbers remain small due to the rarity of the disease; such numbers continue to illustrate the need for multicenter cooperative group trials. Also, following the intention-to-treat principle meant all patients randomized to receive radiation were counted as events, although the published findings of AHOD0031 likely will similar patients in the future (RER) will not receive radiation. Additionally, the small number of late effects precluded meaningful comparisons, although overall the rate was low with both regimens. We were limited to our standard length of follow-up and standard late effect surveillance study results available given the nature of this retrospective chart review. Finally, due to the nature of patient heath documentation maintenance, and the lack of electronic medical records for the patients who were treated in the earlier years, the data collection, such as radiology and outside records, was limited for some.

In conclusion, our study demonstrated that the ABVD and ABVE-PC regimens had similar survival outcomes without excess late effects. We found that patients under the ABVE-PC regimen required more radiation, although the question of radiation randomization in AHOD0031 increased the number of patients receiving ABVE-PC that ultimately required radiotherapy. Nonetheless, the rate of second malignant neoplasms and other late effects appeared to be low.

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Figure Legends

Figure 1 – Event-free survival and overall survival. A: Event-free survival as defined by time to first relapse or last-known follow-up if still in first remission. B: Overall survival, as defined by time to death or to last-known follow-up if still alive. ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine. ABVE-PC: Adriamycin, Bleomycin, Vincristine, Etoposide, Prednisone, Cyclophosphamide

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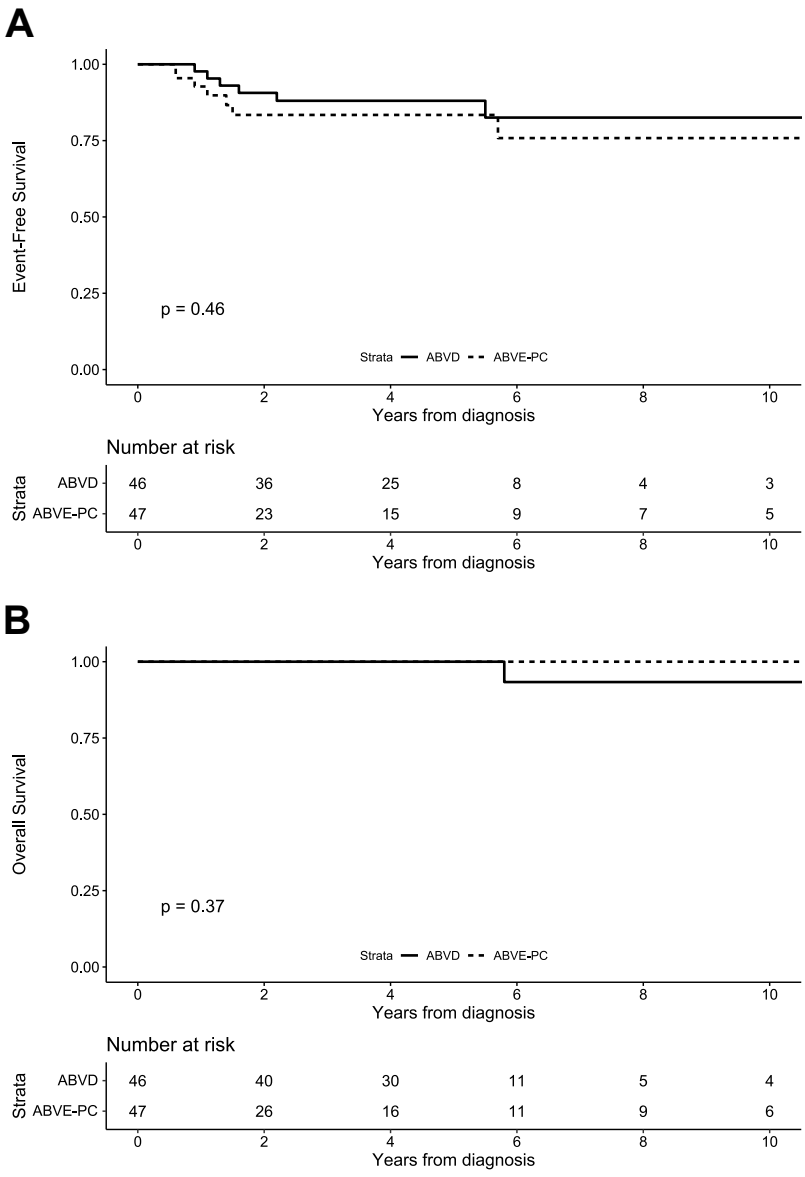

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