Treatment of high-risk Hodgkin Lymphoma with a modified Stanford V regimen in the AHOPCA: substituting chemotherapy agents and hampered outcomes

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Abstract

Background/Objectives: High-risk Hodgkin lymphoma (HRHL) in children is a curable with combined modality therapy. The AHOPCA is a consortium of cancer centers from Central America. In 2004, AHOPCA implemented a guideline with a short course of chemotherapy (mStanfordV), strict diagnostics and radiation guidelines, aimed at reducing abandonment and improving outcomes. Methods: Newly diagnosed children less than 18 years of age with high-risk HL (Ann Arbor stages: IIB, IIIB, IV) from AHOPCA centers were staged with chest X-ray, and ultrasound or CT. Therapy was a modified StanfordV (mStanfordV) substituting cyclophosphamide for mechlorethamine and involved field radiation. Results: Of 219 patients with HRHL, 181 patients were eligible and evaluable; 146 (81%) were boys, 22% being less than 6 years; 43 were stage IIB, 84 IIIB and 54 IV. Thirty-one (17%) abandoned therapy, 28 (15%) progressed, 30 (17%) relapsed and 8 (4%) died of toxicity. Radiation guidelines were not followed. Five-year abandonment-sensitive event-free survival and overall survival (AS-EFS, AS-OS±SE) for the cohort were 46±4% and 56±4%; 5-year AS-OS for stages IIB, IIIB and IV was 76±7%, 59±7%, and 35±7% (p=0.0006). Conclusion: Despite instituting a short treatment guideline, it did not improve the abandonment rate (17%) and did not achieve the reported outcomes of StanfordV. The cyclophosphamide dose used to replace mechlorethamine was inadequate. Despite strict guidelines, the radiation therapy application was inaccurate. Weekly chemotherapy may have adversely affected abandonment of therapy by increasing the burden of travel-time. Based on these results, AHOPCA established a new abandonment strategy and a new guideline.

INTRODUCTION

Hodgkin Lymphoma (HL) is one of the most prevalent tumors (9%) treated at the Association of Pediatric Hematology-Oncology of Central America (AHOPCA), a childhood cancer network of pediatric cancer institutions in Central America. It is a disease of the immune system characterized by the proliferation of malignant cells, known as Reed-Sternberg cells, which cause damage to the normal tissues and organs. The treatment of HL involves a combination of chemotherapy, radiation therapy, and in some cases, autologous stem cell transplantation. The goal of treatment is to cure the disease while minimizing the impact of therapy on the patient's quality of life. However, achieving these objectives can be challenging due to the complexity of the disease and the need for interdisciplinary care.
centers from Central America, Dominican Republic, and Haiti\textsuperscript{1}. This network designs uniform treatment guidelines, for children with cancer diagnosed at the individual centers. Over time, AHOPCA has studied baseline treatment outcomes for different pathologies in the region, and has addressed unique psychosocial needs in low- and middle income countries (LMIC)\textsuperscript{1,2}. Because radiation therapy is not easily accessible in every country in Central America, the AHOPCA Center in Nicaragua designed a chemotherapy only regimen consisting of four cycles of cyclophosphamide, vincristine, prednisone and procarbazine (COPP) for patients with early stage HL and two to four additional courses of chemotherapy consisting of doxorubicin, bleomycin and vinblastine (COPP/ABV) for advanced stage HL\textsuperscript{3}. Based on encouraging results for this regimen, AHOPCA implemented a chemotherapy-only treatment guideline\textsuperscript{4}: AHOPCA LH-1999 using the same risk assessment and treatment schema for all subjects presenting to an AHOPCA Center. Castellanos et al reported an event-free survival (EFS) of 60\% regardless of risk assignment\textsuperscript{4}. However, the EFS for patients with Ann Arbor stage IV HL was only 20\%. This report identified two critical factors that influenced the poor outcomes: abandonment of therapy (13\%), accuracy of diagnosis and appropriate staging\textsuperscript{4}.

To improve survival, improve diagnostic accuracy and reduce abandonment, AHOPCA introduced in 2004 three risk groups, low, intermediate, and high with strict staging and risk assignment criteria, response assessment and clear radiation therapy guidelines. AHOPCA hypothesized that a regimen that could be administered over a short period of time (to prevent abandonment), that had an established low toxicity profile with lower anthracycline dose (150mg/m\textsuperscript{2}), and low infertility\textsuperscript{5}, would be effective in a resource-limited setting. Based on the excellent results reported with the Stanford V regimen\textsuperscript{5 6}, a short 12-week course of chemotherapy with doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone and mechlorethamine and 36 Gy radiotherapy to bulky sites of disease (> 5cm) at diagnosis. AHOPCA adopted this regimen as a treatment guideline for children presenting with pre-defined high-risk HL (HRHL). In 2004 there was a world-wide shortage of mechlorethamine\textsuperscript{7}, leading AHOPCA to modify the treatment regimen substituting mechlorethamine with cyclophosphamide at a dose that was expected to be an equipotent substitution. Furthermore, radiation therapy was modified to (20-25 Gy) involved field in order to limit radiation-related long-term effects\textsuperscript{8-10}. We report here the experience of AHOPCA with this regimen, AHOPCA HRHL 2004 (mStanford V), as applied between August 2004 and August 2009.

\section*{METHODS}

The treatment guidelines were implemented as standard of care and not research, as the adaptation was felt to be necessary to fit the resources of the region. The guidelines were approved according to institutional requirements, and general treatment consent was obtained from the legal guardians.

\subsection*{Subjects}

AHOPCA HRHL 2004 enrolled subjects between January 2004 and August 2009. Consecutive patients, less than 18 years of age, with histologically confirmed previously untreated high-risk (Table 1s); defined as modified Ann Arbor stages IIB, IIB and IV, irrespective of bulky disease [mediastinum > 1/3 diameter, or peripheral lymph nodes greater then 6cm]) HRHL (classical and nodular lymphocyte predominant) presenting to one of the AHOPCA centers (El Salvador, Guatemala, Honduras, Nicaragua and Dominican Republic), were treated according to the guidelines and are the subject of this report. Patients previously treated for HL or seropositive for the human immunodeficiency virus were excluded. As a treatment guideline to improve quality of diagnosis and treatment, all countries consented for therapy according to the local policies.

Prior to starting therapy, all patients underwent a complete medical history, physical examination and evaluation by imaging and laboratory studies consisting of complete blood cell count, erythrocyte sedimentation rate (ESR), blood chemistries including renal and liver function studies, and albumin. All underwent an excisional biopsy from an easily accessible lymph node or a "trucut" biopsy of the mediastinum or abdominal mass. Pathology was reported for El Salvador, Guatemala and Dominican Republic with immunohistochemistry’s (CD30, CD15, CD20) to confirm diagnosis of HL (classical histology or nodular lymphocyte predominant). Honduras and Nicaragua reported diagnosis using morphology only. Patients with B symptoms or advanced
disease had a bilateral bone marrow biopsy performed.

**Imaging and Laboratory Evaluation**

Imaging studies included two-view chest x-ray, contrast enhanced neck, chest, abdominal and pelvic computed tomography (CT). Patients who could not have a CT scan (they were too ill, or CT was not available) had an evaluation with an ultrasound of the neck, axilla, abdomen, pelvis and inguinal regions. There was a response assessment at the end of 12-week chemotherapy and after completion of radiation therapy.

**Treatment Regimen**

The mStanford V regimen (Table 2s) consisted of chemotherapy for 12 consecutive weeks followed by involved-field radiation therapy (IFRT). The chemotherapy was: prednisone 40mg/m2 orally divided bid every other day for 10 weeks followed by a 2 week taper, doxorubicin 25 mg/m² and vinblastine 6 mg/m² on weeks 1, 3, 5, 7, 9 and 11; cyclophosphamide 600 mg/m² on weeks 1, 5 and 9; vincristine 1.4 mg/m² (maximum of 2mg) and bleomycin 5 U/m² on weeks 2, 4, 6, 8, 10 and 12 and etoposide 60 mg/m² on days 1 and 2 of weeks 3, 7 and 11. The modification from the original Stanford V regimen, consisted of the substitution of cyclophosphamide 600 mg/m²/dose, instead of mechlorethamine 6mg/m²/dose. Radiation therapy (cobalt unit or linear accelerator) was administered to all originally involved sites of disease according to their response to chemotherapy at either 2000cGy to the sites that achieved an anatomic complete remission (> 80% reduction of the sum of the perpendicular diameters or return to normal size lymph nodes) or 2500cGy to the sites that did not achieved a complete remission. Chemotherapy was held for 1 week if ANC was less than 1000 and/or platelets less than 100,000 on the weeks that included doxorubicin. All patients received pneumocystis jovenci prophylaxis with trimethoprim/sulfamethoxazole. Some units were able to give filgrastim to patients with prolonged neutropenia and infection at the discretion of the local treating physician and availability of the drug. All members met weekly by video conference through www.cure4Kids.org to discuss problem cases.

**Response Criteria**

Two weeks after completion of chemotherapy, all subjects had imaging studies to evaluate response. We defined the level of response as: a complete remission (CR) if there was complete disappearance of all sites of disease (as evaluated by physical examination and imaging studies) and B symptoms. Partial remission (PR), defined as disappearance of all constitutional symptoms and decrease of [?] 50% of the sum of the product of two perpendicular diameters of all lesions present at diagnosis and no appearance of new lesions. No response (NR) defined as no change or <50% decrease in the product of two perpendicular diameters of any lesion present at diagnosis without new lesions. Progressive disease (PD), defined as increase of [?] 50% of the product of two perpendicular diameters of any lesion or the appearance of new lesions during therapy or within 3 months of end of radiation therapy. Relapse (R), defined as appearance of new lesions after 3 months from end of radiation therapy confirmed by biopsy in most cases.

**Data Management and Statistical Analysis**

Data were collected prospectively and entered by the local center’s data manager into the database POND (Pediatric Oncology Network Database) (this database was retired in 2019). Data frozen as of December 31st 2017 are included in this report. The data were reviewed and confirmed by the primary country team and the PI, with constant quality reviews. Abandonment of therapy was defined as failure to return to continue treatment for 4 weeks or more. Lost to follow-up was defined as 2 years from the end of therapy. Upfront refusals were excluded from the analysis.

Primary outcomes were abandonment-sensitive event-free survival (AS-EFS) and abandonment-sensitive overall survival (AS-OS). AS-EFS was defined as the time from date of diagnosis to date of first event (progressive disease, relapse, abandonment, or toxic death) or date of last contact for those who were event-free. AS-OS was calculated as time from diagnosis to abandonment or death, or last contact for those still alive. In addition, EFS and OS rates censoring abandonment, were also calculated. Survival rates were estimated using the Kaplan-Meier method with standard errors of Peto et al. The two-sided log-rank
test was used for comparison of survival curves. P-values <0.05 were considered statistically significant for all comparisons. All analyses were performed using SAS® version 9.4. Graphics were generated using R (http://www.R-project.org, version 4.1.1).

RESULTS

Demographics
A total of 219 patients with HRHL were referred to the participating AHOPCA centers. Seven patients were not eligible because of prior therapy (n=6) or being HIV positive (n=1). Thirty-one were not evaluable: 20 treated with a different regimen, 6 refused therapy, 4 had a wrong stage, and 1 died before starting therapy. One hundred eighty-one patients were evaluable for this report (Figure 1).

Table 1 summarizes demographic data for all subjects. The median age at presentation was 9 years (range 3-18 years). Twenty-two percent (n=39) of subjects were younger than 6 years of age at diagnosis, 37% were ages 6 to 10 (n=67) and 41% (n=75) were 10 or older. There were 146 (81%) males. The predominant histologic subtype was mixed cellularity in 80 (44%), followed by nodular sclerosis 77 (43%), lymphocyte predominant in 11 (6%), lymphocyte depleted in 6 (3%) and in seven (4%), the histologic subtype was not specified. The distribution of stage at diagnosis was stage IIB 43 (24%), IIIB 84 (46%), IVA 4 (2%) and IVB 50 (28%).

Chemotherapy and response
Of the 181 patients, thirty patients did not complete chemotherapy: 21 abandoned therapy, 7 died during therapy (6 infection and 1 PD), and 2 PD (taken off protocol). 151 patients proceeded to response evaluation; of them 66 (44%) had CR, 71 (47%) had PR, 4 (3%) had PD (taken off therapy), and 10 (7%) did not report the response evaluation (Table 2).

Radiation therapy
Of the 151 patients who continued on therapy, the 4 had PD, 1 progressed while waiting for radiation, 1 relapse (refused radiation and relapsed 11 months after the end of chemotherapy), and 8 abandon therapy after response evaluation were taken off protocol therapy (Figure 1). Of the 137/151 (91%) who proceeded to receive radiation therapy after chemotherapy, 110 (80%) received radiation therapy on time, 25 (18%) started radiation more than 2 months after completion of chemotherapy, 2 (2%) abandoned therapy during radiation. Of the 135 who completed radiation, 16 (12%) did not get radiation to all involved sites. Forty-eight (36%) were given the incorrect dose: 39 (29%) was too high (2700-5040cGy), and 9 (7%) too low (1500-1800CGy). Of the 87 who received radiation within the correct dose range: 11 received the incorrect dose assigned according to CR (n=8) or PR (n=3).

Abandonment of therapy
A total of 31/181 (17%) patients abandoned therapy: 21 during chemotherapy, 8 before radiation therapy, and 2 during radiation therapy. Of the 31, 19 (61%) patients never returned. Of the twelve that returned: 8 returned in relapse or progressive disease. Among these 12, five restarted mStanfordV therapy (chemotherapy and radiation) and one received only radiation. Last status of these 12 returned patients are: 6 expired (4 months to 7 years from diagnosis), 2 abandoned therapy second time (17 and 33 months from diagnosis to last contact), 1 lost to follow-up in CR (5 years from diagnosis to last contact), and 3 alive (8 to 11 years from diagnosis to last contact).

Toxic deaths
Of the 181 patients that started therapy, 8 (4%) had a toxic death event. Of these, 7 were during chemotherapy, and one expired after radiation therapy. There were delays in chemotherapy, but none more than 2 weeks; except 1 patient who changed to a different protocol (at the investigator’s choice) as the family could not attend weekly.

Outcomes
Of The 181 patients who started therapy, 135 completed chemotherapy and radiation therapy. Of the 181 patients, 97 (54%) experienced an AS-EFS event: 31 (32%) abandoned therapy, 28 (29%) progressed, 30 (31%) relapsed and 8 (8%) died of toxicity. The median follow-up for the patients who are alive and have not abandoned therapy, is 8 years (range 0-12 years).

The 5-year AS-EFS and AS-OS for the 181 eligible and evaluable patients were, 46 ± 4% and 56 ± 4%, respectively (Figure 2A). The 5-year EFS and OS for the cohort, were 54 ± 5% and 69 ± 4%, respectively (Figure 2B). The 5-year AS-EFS rates by stage were: stage II 65 ± 8%, stage III 52 ± 7%, and stage IV 22 ± 6% (p=0.0001) (Figure 3A). The 5-year AS-OS rates by stage were: stage II 76 ± 7%, stage III 59 ± 7%, and stage IV 35 ± 7% (p=0.0006) (Figure 3B). When abandonment is censored, 5-year EFS rates by stage were: stage II 73 ± 8%, stage III 62 ± 7% and stage IV 25 ± 7% (p<0.0001) (Figure 4A); 5-year OS rates by stage were: stage II 87 ± 6%, stage III 74 ± 6%, and stage IV 43 ± 8% (p<0.0001) (Figure 4B).

DISCUSSION

We report herein the results of the AHOPCA LH 2004, a prospective treatment regimen for children presenting with histologically proven high-risk HL, Ann Arbor stages IIB, IIB and IV, which accrued patients from January 2004 through August 2009. The guideline offered a modified, short and effective therapy (mStanford V) with the aim of limiting late effects, improve outcomes and decreasing abandonment of therapy through a faster chemotherapy regimen. However, abandonment of therapy continued to be high at (17%) without improvement in survival: 5-year AS-EFS and AS-OS were 46 ± 4% and 56 ± 4%; 5-year AS-EFS EFS by stage were stage II 65 ± 8%, stage III 52 ± 7%, and stage IV 22 ± 6% (p=0.0001).

The AHOPCA LH 2004 cohort confirmed that HL in low and middle-income countries (LMIC) presents at an earlier age than HIC. With a median age at presentation of 9 years and 22% were less than 6 years of age, the AHOPCA LH 2004 cohort was slightly older than the previous cohort (7.5 years) reported5, but younger than the median age of 15.8 years reported by the Children’s Oncology Group (COG)16 and median age of 14.8 years from the EuroNet PHL-C117. Moreover, percentage of very young children (less than 6 years old: 22%; less than 10 years old 59%); and the high proportion of males in our cohort (81%), differs from the proportions reported in HIC (53-56%)16,17. The predominant histology (44%) was mixed cellularity, which is higher than the 6% reported by the COG16.

Most patients tolerated the mStanford V regimen well. However, the toxic death rate (4%) is high, as one (0.0007%) reported by EuroNet PHL-C1 group17 and none COG study16.

Our aim, to decrease abandonment of therapy using a therapeutic regimen with a shorter duration and of easy administration, was not successful. The rate of abandonment (17%) was higher than the 13% from our previous report4. We hypothesized that a short course of chemotherapy would be a relief for the families, and decrease abandonment. However, having to come to clinic once a week, especially for those that need to travel long, may be a stressor. So, despite the shorter regimen and decreased toxicity, travel time may impact family burden and increase abandonment of therapy, as described previously18.

The 5-year AS-EFS of all patients on the current cohort is 46 ± 4%, which is lower than the ten-year AS-EFS of 57±7% for the high-risk group of our previous report 4. However, the current report has a higher proportion of subjects with stage IV disease (30%) than the previous report (5%)4. When we compared the AS-EFS by stage, the AS-EFS in the current cohort is significantly affected by the 17% abandonment, a prevalent and psychosocial reality in many LMIC 18,19. However, if those patients who abandon therapy are censored, the OS appears better than the previous study: OS for stage II 87 ± 6%, stage III 74 ± 6%, and stage IV 43 ± 8% . Nonetheless, these results are inferior to the results reported for the original Stanford V regimen in adults5,6 and most recent report in children7.

Due to the worldwide shortage of mechlorethamine, a drug modification of Stanford V, using cyclophosphamide at 600mg/m² was not equipotent to the doses used in the original regimen. As reported by Metzger et al7, subjects treated with cyclophosphamide on the modified Stanford V protocol, had a two-year EFS of 75% vs 88% for those treated with mechlorethamine, impacting outcomes negatively. Substituting chemothe-
The use of therapeutic drugs is a frequent practice in LMIC, where essential medicines for childhood cancer are either not offered by the country, are frequently in short supply, or are too expensive. To the best of our knowledge, the chemotherapy regimen was given in a timely manner, without deviation in dosing or time in our cohort.

The second modification we introduced was reduction of the total dose of radiation therapy from the original protocol (3600cGy). Although it is possible that this substitution may have contributed to the poorer results, other pediatric treatment regimens use 15 to 25 Gy in a response adapted fashion. The same treatment regimen used by the St Jude - Dana-Farber-Stanford- consortium had a better outcome than ours, utilizing radiation therapy doses of 1500-2500Gy confirmed an EFS of 75%. Our cohort suffered significant deviations in regards to the radiation therapy administration. Twelve percent did not irradiate all involved sites, and 36% gave the incorrect dose. We did not assess the effect of dose or field deviations from the guidelines. The variability of dose and the delay in administration of radiotherapy could have affected EFS for our cohort. Furthermore, 18% had a delay of greater than 2 months in administration of radiation after end of chemotherapy; yet, we could not demonstrate a statistical difference between those patients that received their radiation therapy on time and those with a delay in administration.

There are 2 important lessons learnt by this experience: a) the change of chemotherapeutic agents of well-established and known regimens (due to local or global shortage or stock-outs of drugs) may lead (as in this guideline) to increased toxicity, more abandonment, and worse outcomes; and b) access to radiation therapy for childhood cancer, with timely planning and adequate dosing and administration are essential to guarantee good clinical outcomes. These described failures pose a significant weakness of the guideline study, where the regimen was changed, not followed as written; and quality assurance not provided in real-time.

AHOPCA continues to look to improve the survival outcome of their patients and to decrease abandonment of therapy. To this effect, they have developed group-wide and comprehensive psychosocial interventions to decrease and understand abandonment; and have implemented a new therapeutic approach to improve EFS and OS in children with HRHL.

We hope that the results of this guideline study, aiming to improve outcomes, serves as an example for LMIC, that changes or adaptations of regimens (due essential medicines shortage or lack of implementation of WHO EML list in the country), can be detrimental. An organized and systematic approach to childhood cancers with continuous evaluation of outcomes and coordinated implementation science methods and strategies can improve the lives of these children. This is why, in 2020, World Health Organization (headquarters and the regional offices) in conjunction with partners around the world (St Jude Global, St Jude Children’s Research Hospital, and the International Society of Pediatric Oncology [SIOP]), members of the multidisciplinary teams (pediatric oncologists, surgeons, nurses, radiation therapists, psychologists, etc.), advocacy organizations (SIOP, local non-governmental associations that help families of children with cancer), and country governments (through ministries of health and cancer control programs), have instituted the Global Initiative for Childhood Cancer, using the CureALL framework, to make comprehensive diagnosis, appropriate treatment and continuous outcomes measures, not only accessible, but financially feasible for all children around the world, to be treated, cared and supported, through their diagnosis of childhood cancer and into survivorship (https://apps.who.int/iris/handle/10665/347370).

Conflict of interest: the authors of this manuscript do not have any conflict of interest.

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REFERENCES


**Figure Legends**

**Figure 1.** AHOPCA LH 2004 High-Risk Consort Diagram

**Figure 2.** Survival curves for entire cohort. **Panel A:** 5-year AS-EFS and AS-OS curves. **Panel B:** 5-year EFS and OS curves.

**Figure 3.** AS-EFS and AS-OS curves by stage II, III and IV. **Panel A:** 5-year AS-EFS by stage II, III and IV. **Panel B:** 5-year AS-OS by stage II, III and IV.

**Figure 4.** EFS and OS curves by stage II, III and IV. **Panel A:** 5-year EFS by stage II, III and IV. **Panel B:** 5-year OS by stage II, III and IV.

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