Management Considerations of Hodgkin Lymphoma for Patients with Fontan Physiology

Michelle Perry Milligan[1] and Leslie Kersun[1]

[1]The Children's Hospital of Philadelphia

November 18, 2021

Abstract

While treatment protocols for Hodgkin Lymphoma (HL) are well established, there is no literature available to guide therapy or estimate prognosis for patients with Fontan physiology who develop HL. The physiology of a Fontan procedure can result in the inability to tolerate chemotherapy toxicities, supportive care and infection. We present a series of 3 patients with Fontan physiology who were treated for HL and discuss their clinical course and treatment.

Management Considerations of Hodgkin Lymphoma for Patients with Fontan Physiology

Authors: Michelle C Perry Milligan MD [a], Leslie S Kersun MD, MSCE, MSEd [a, b]

Affiliations: [a] Division of Oncology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.[b]Perelman School of Medicine at the University of Pennsylvania

Corresponding Author: Michelle Milligan

Division of Oncology 3401 Civic Center Blvd, Philadelphia, PA 19104.

Email: perrymillm@chop.edu

Word Count

Abstract: 70

Main Text:1173

Tables, Figures and Supporting Information files: 0

Short Running Title: HL Treatment for Patients with Fontan Physiology

Keywords: Hodgkin Lymphoma, Lymphoma, Hodgkin's Disease, Fontan Physiology

Abbreviations Table

AVE-PC	Adriamycin, vincristine, etoposide, prednisone, cyclophosphamide
ANC	Absolute neutrophil count
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine
Bv	Brentuximab vedotin
EBV	Epstein-Barr virus
ECMO	Extracorporeal membrane oxygenation
E-COPP + R	Etoposide, cyclophosphamide, vincristine, prednisone, procarbazine, rituximab
HL	Hodgkin Lymphoma

AVE-PC	Adriamycin, vincristine, etoposide, prednisone, cyclophosphamide
IVIG	Intravenous immune globulin
PICC	Peripherally inserted central catheter
PJP	Pneumocystis Jiroveci Pneumonia
SVT	Supraventricular tachycardia
VE-PC + Bv	Vincristine, etoposide, prednisone, cyclophosphamide, brentuximab

Abstract

While treatment protocols for Hodgkin Lymphoma (HL) are well established, there is no literature available to guide therapy or estimate prognosis for patients with Fontan physiology who develop HL. The physiology of a Fontan procedure can result in the inability to tolerate chemotherapy toxicities, supportive care and infection. We present a series of 3 patients with Fontan physiology who were treated for HL and discuss their clinical course and treatment.

Introduction

Hodgkin Lymphoma (HL) is treated with well-established chemotherapy regimens.[1-3] Patients with Fontan physiology require special considerations when planning chemotherapy because their physiology cannot tolerate particular toxicities or usual stresses associated with treatment.[4] Many of the combinations used for HL include anthracycline with the possibility for cardiac toxicity, bleomycin with the risk for pulmonary fibrosis and cyclophosphamide necessitating additional fluid boluses and hydration. There are no recommended guidelines for treating patients with Fontan physiology who have developed lymphoma or other types of cancer. Additionally, there are no published data demonstrating increased risk for these patients or if their prognosis deviates from HL patients without cardiac disease. The aim of this article is to review the clinical course of three patients with Fontan physiology who developed HL and to discuss the alterations of treatment considered by the oncology and cardiology teams in the design of their chemotherapy regimens.

Case Summaries

Patient 1 was born with double outlet right ventricle, palliated with a Fontan procedure. As a complication of Fontan physiology, she developed chronic protein-losing enteropathy. At the age of 18, she developed intermittent fevers and cytopenias which was ultimately diagnosed as stage IVB HL (EBV+). IgG level at diagnosis was 48.

A modified BEACOPP-like therapy regimen (E-COPP + R) X 6 was utilized. (Etoposide, cyclophosphamide, vincristine, prednisone, procarbazine, rituximab). Bleomycin was eliminated to avoid pulmonary fibrosis. Adriamycin was eliminated due to the potential for acute cardiac toxicity. She received 5 cycles of this regimen administered via PICC and had a complete response after 2 cycles. All cycles were followed by peg-filgrastim. She received IVIG approximately every 2 weeks. She developed a pneumonia requiring positive pressure respiratory support and treated with antibiotics following cycle 1. On day 9 of cycle 5, she presented to the emergency department with fluid overload and abdominal pain. Her ANC was 100 mm^3 on admission. She was diagnosed with multi-organ dysfunction caused by gram negative sepsis. Despite antibiotics, aggressive fluid resuscitation and vasopressor therapy, she suffered a cardiac arrest on hospital day 2 and ventricular-arterial ECMO was initiated. She required hemodialysis on hospital day 3. She died that day after her family chose to withdraw technologic support.

Patient 2 was born with hypoplastic left heart with double outlet right ventricle. He underwent lateral Fontan procedure. At age seventeen, he presented with cough, fever, night sweats and abdominal distension. Medical evaluation revealed hilar lymphadenopathy, and biopsy demonstrated HL (EBV+), stage IIB.

He was treated with AVE-PC (doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide, + Rituximab via PICC. In discussion with his cardiologist, doxorubicin dose was reduced. Bleomycin was excluded to avoid pulmonary fibrosis. After cycle 2, echocardiogram showed worsening single ventricle function.

Subsequent therapy eliminated doxorubicin and ventricular function stabilized. Supportive care included Peg-filgrastim and bactrim for Pneumocystis Jiroveci Pneumonia (PJP) prophylaxis. He was admitted once for neutropenic fever without infectious source. He had a complete response to therapy, however relapsed 7.5 years later.

Patient 3 was born with dextrocardia-asplenia syndrome, complete common AV canal with RV-aorta and pulmonary atresia. He underwent the lateral Fontan procedure. Other chronic health issues included SVT S/P ablation, chronic hepatic congestion and lifelong penicillin prophylaxis for asplenia without any infections. At 24 years of age, he noted several months of cervical lymphadenopathy and biopsy demonstrated HL (EBV+), stage IVA.

Anthracycline was excluded for potential cardiotoxicity, and bleomycin was excluded to avoid pulmonary fibrosis. He was treated with VE-PC + Bv (vincristine, etoposide, prednisone, cyclophosphamide, brentuximab) through a peripheral IV. Cycles were followed by peg-filgrastim. He continued penicillin prophylaxis during his therapy and changed to levofloxacin during periods of neutropenia given risk for opportunistic infection and concern that he would not tolerate sepsis. Treatment course was complicated by two episodes of febrile/neutropenia without infection identified and multiple episodes of SVT resolved by vagal maneuvers or adenosine. He had a complete response to therapy and is clinically well, two years post treatment.

Discussion

Therapy was carefully designed for these patients with recognition that their physiology would limit the tolerance of standard cancer therapy. This required modifications to the chemotherapy and supportive care including fluid management, anti-emetics and venous access. In collaboration with cardiologists, anthracyclines were removed or dose-reduced due to the potential risk of cardiotoxicity, and bleomycin was eliminated because of its risk of pulmonary fibrosis. Although rare, pulmonary fibrosis would not allow the Fontan to function given the required passive pulmonary flow.

Supportive care required careful consideration. All patients received cyclophosphamide that requires fluid bolus and brisk hydration to prevent cystitis. Although the dose did not require Mesna for bladder protection, Mesna was prescribed for all patients given fluid modifications. Boluses were given slowly and the rate of hydration was decreased compared to standard operating procedures. Anti-emetic medications were not restricted, but were monitored with telemetry in order to ensure there was no QTc prolongation.

Additionally, the anatomy of the vasculature and heart after a Fontan procedure is not compatible with placement of a central venous catheter. The available access option of a PICC increases risk of infection. Patient 1 and 2 had PICCs placed at the initiation of therapy and also received anticoagulation given the concern for thrombosis. At the time, anticoagulation was standard practice for all patients with congenital heart disease and PICC. Patient 3 received all therapy through a peripheral IV.

Finally, the infectious risk was also perceived to be greater for some and their ability to physiologically compensate for sepsis was impaired compared to a standard patient. Patient 1 was further immunologically compromised by protein-losing enteropathy and received PJP prophylaxis, monthly IVIG and peg-filgrastim. Unfortunately, she died from sepsis. Patient 2 also received peg-filgrastim, PJP prophylaxis and had no infectious complications. Patient 3 had congenital asplenia and received lifelong penicillin, PJP prophylaxis and peg-filgrastim. Given the concern for overwhelming bacterial infection and risk for sepsis based on our experience with patient 1, our team replaced his penicillin with levofloxacin for broader antibacterial coverage during periods of neutropenia.

There are a variety of treatment regimens that could be utilized in this situation. We used the contemporary chemotherapy protocol for high-risk HL at the time of each diagnosis and made modifications with extensive discussion with cardiologists. It is difficult to determine prognosis when there is substantive alteration of the chemotherapy treatment. Our approach was to use the most reasonable regimen with elimination of the medications that had too great a risk of acute or later toxicity. Brentuximab vedotin (Bv) and use of targeted treatments may mitigate toxicity and allow less toxic agents to be substituted or added to these

modified chemotherapy regimens.[5] Additionally, we monitored each patient closely for response and all had a complete response after 2 cycles with reasonable tolerance of the regimen. We also carefully considered every aspect of supportive care to minimize known toxicity and infection. Unfortunately, one of our patients did not survive despite her excellent response. This treatment can be undertaken in close consultation with cardiology colleagues, attention to supportive care and individual tailoring for every patient given physiology, other health history, chronic health conditions and potential for side effects.

Conflict of Interests: Dr. Michelle Perry Milligan and Dr. Leslie Kersun have no conflicts of interest to disclose.

Acknowledgements: We owe a debt of gratitude to our patients for everything that we have learned by caring for them. We thank Dr. Jack Rychik and Dr. Yuli Kim for their contributions in caring for these patients and discussions in preparation of this case series. This project was not supported by a funding source.

1. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol.*2014;32(32):3651-3658.

2. Kelly KM, Sposto R, Hutchinson R, et al. BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: a report from the Children's Oncology Group.*Blood.* 2011;117(9):2596-2603.

3. Kelly KM. Management of children with high-risk Hodgkin lymphoma.*Br J Haematol.* 2012;157(1):3-13.

4. Guinan EC, Hewett EK, Domaney NM, Margossian R. Outcome of hematopoietic stem cell transplant in children with congenital heart disease. *Pediatr Transplant.* 2011;15(1):75-80.

5. Schieszer J. FDA Approval of Brentuximab Vedotin With Chemo Offers New Hope for Stage III/IV Hodgkin Lymphoma. March 22, 2018, 2018.