Primary Thromboprophylaxis to Prevent Thrombotic Events in Pediatric Oncology Patients with a Malignant Mediastinal Mass.

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March 15, 2021

Abstract

Children with malignant mediastinal masses have increased thrombotic events (TE). We examined primary thromboprophylaxis in reducing TE. Eligible subjects were started on enoxaparin thromboprophylaxis and compared to a cohort without. There were 15 TEs among 76 subjects for an incidence of 19.7%. Mediastinal compression directly led to TE, (M-TE) in 9.2% of subjects requiring 2-fold longer duration of therapeutic anticoagulation. Primary thromboprophylaxis revealed a trend towards reduction in M-TE although not statistically significant. The M-TE subjects had greater superior vena caval compression at diagnosis (p=0.033). We conclude that strategic thromboprophylaxis guided by monitoring dynamic vascular compression can improve TE outcomes.

Introduction

The role of primary thromboprophylaxis in children with cancer is not clearly delineated despite a distinct risk of thrombosis. Children with cancer have a 600 -fold higher risk of thrombotic events (TE) with a prevalence of 1-37% in acute lymphoblastic leukemia [2, 3], 12% in lymphomas and 8-14% in sarcomas [1]. A malignant mediastinal mass poses unique challenges given proximity to vital structures causing vascular compression and stasis. Central venous lines (CVLs) in this area further heightens this risk due to vascular intimal damage. Up to a third of patients can develop post thrombotic syndrome with significant morbidity in patients who otherwise have excellent outcomes with multi-agent therapy [1, 4].

Pediatric guidelines recognize mediastinal tumors as a TE risk factor but only suggest primary thromboprophylaxis in the presence of combinatorial risk factors [5]. However, the incremental risk of TE warrants exploration of primary thromboprophylaxis in TE prevention in children and young adults with malignant mediastinal masses. Furthermore, the relationship of dynamic mediastinal vessel compression during the treatment course may serve as a guide to the duration of thromboprophylaxis.

Methods

After Northwell Health Institutional Review Board approval, a retrospective chart review was conducted of patients (0-21years) with a malignant mediastinal mass at diagnosis (ICD 9 786.6/ICD 10 R22.2) ascertained from the pathology and radiology data bases and corroborated using the oncology database at Cohen Children's Medical Center from January 2000 to December 2017. All patients received chemotherapy per Children's Oncology Group protocols. Demographic data including age, sex, type of cancer and CVL were recorded. The TE was attributed to the mediastinal mass (M-TE) if the vessels involved by the TE were compressed by the mass on imaging.

Patients with a malignant mediastinal mass were started on primary thromboprophylaxis with enoxaparin (1.5 mg/kg) subcutaneously daily without anti Xa monitoring which after 2013 became standard of practice at our institution. Thromboprophylaxis was discontinued when the mass showed >50% reduction on imaging following chemotherapy. The study radiologist blinded to the thromboprophylaxis status evaluated the extent of mediastinal vessel compression and presence of collateral vessels. The degree of vessel compression in the largest affected vessel was calculated as a percentage, utilizing the maximum diameter of this vessel on follow up scan and subtracting the narrowest diameter on the diagnostic scan at the same plane (Figure 1). An independent radiologist reviewed the data set and inter-observer concordance was evaluated.

Descriptive statistics (mean, median, standard deviation for continuous variables; frequencies and proportions for categorical variables) were calculated. The Fischer's exact test or Pearson's chi-squared test was used to evaluate the association between groups and demographic and clinical variables. The incidence of M-TE was calculated and the odds ratio with 95% confidence interval (CI) for developing M-TEs was estimated between the prophylaxis vs non – prophylaxis groups. Superior vena cava (SVC) compression was compared between the M-TE and non-M-TE subjects.

Results:

A total of 93 subjects met study criteria; 17 were excluded due to unavailable follow up imaging. The mean age was 14.6 + 3.2years with 39 (51.3%) males and 37 (48.7%) females. Cancer diagnoses included Hodgkin lymphoma (51, 67.1%), non-Hodgkin lymphoma (16, 21.1%), T cell lymphoma (7, 9.2%) and other cancers (2, 2.6%). Mediastinal compression of multiple vessels was found in 75% of subjects (n=57/76) at diagnosis. A fourth (n=19/76) received primary thromboprophylaxis of which only 2 had no evidence of vessel compression. The overall TE incidence was 19.7% (n= 15/76) from all causes but related to M-TE in 7 subjects (9.2%) (Supplemental Table 1). Among the M-TE subjects, only 1 subject was on thromboprophylaxis and developed a TE due to inadvertent discontinuation of thromboprophylaxis despite ongoing compression. The odds of developing M- TE while on primary thromboprophylaxis was 0.47 but not significantly different from those not on prophylaxis (95% CI: 0.05 - 4.19, P= 0.5). Half of the TEs (n=8/16) were related to the presence of a CVL (2 in the prophylaxis and 4 in the non-prophylaxis group)(Supplemental Table 1). The mean time of the TE was 84.3+ 66 days from diagnosis but was shorter (16.14+ 37 days) in the M-TE group with 71% (n=5/7) detected at diagnosis (p=0.009).

Vascular compression most affected the SVC and brachiocephalic veins. The SVC compression at diagnosis was greater in the M-TE versus the non–M-TE group (p= 0.033) (Table 1). The mean percentage of vascular compression at diagnosis was 50.2+ 31.9 % which decreased to 10.5+ 22.5 % on follow up scans (p<0.001). Three fourths (76.7%) of vessels compressed at diagnosis were completely decompressed at follow up. The presence of collaterals or the number of vessels compressed was not associated with TE status. Inter-observer reliability according to Landis-Kosch interpretation of agreement coefficients between the 2 radiologists was between 0.8-1 (almost perfect agreement).

Primary thromboprophylaxis was started within 5 days of cancer diagnosis (median: 49 days). However, subjects with TE needed therapeutic anticoagulation for a median of 96 days. There were no missed anticoagulation doses or bleeding complications.

Discussion:

Data on primary thromboprophylaxis in oncology patients with CVLs generally do not support their systematic use. However one study in adults has shown a reduction in the incidence of TE from 6.8% to 3.7% (p<0.001) with prophylaxis [6] This confirms decades old data on thromboprophylaxis in 25 adults with a malignant mediastinal mass where a similar difference in TE incidence was seen (5/10 TEs in non -prophylaxis group and 0/15 in the prophylaxis group) [7]. In our study we observed a trend towards reduction in M-TE with primary thromboprophylaxis but was not statistically significant likely related to small cohort size. Furthermore, mediastinal mass associated TE incidence of 8.5%, has been reported with the odds increasing by 2.2 when the SVC was >25% compressed[8]. This is akin to our incidence of 9.2% with observed increase in SVC compression with M-TEs versus those without. Therefore, this warrants consideration of primary

thromboprophylaxis in the presence of malignant mediastinal masses with vascular compression. The retrospective study design, small cohort size and lack of thrombophilia data, preclude an accurate estimate of TE. However, our study revealed that primary thromboprophylaxis is safe, vessel compression is dynamic, which can be assessed radiologically with good inter-observer agreement and resolves within 90 days. Our data further supports tailoring the duration of thromboprophylaxis during heightened mediastinal vasculature vulnerability by calculating the degree of vessel compression (Figure 1). This was evident in the one patient on primary thromboprophylaxis with M-TE due to the premature inadvertent discontinuation of anticoagulation despite vascular compression. Subjects developing TEs received therapeutic anticoagulation for twice the duration increasing morbidity, anxiety, discomfort, and overall costs. Clearly, larger studies are needed to formulate thromboprophylaxis guidelines during amplified thrombogenic periods as in mediastinal cancers. Our rationale to adopt systematic primary thromboprophylaxis was corroborated by evidence of local compression of mediastinal vessels in addition to known stasis, inflammation and hypercoagulable state associated with malignancy supported by imaging criteria in determining duration of thromboprophylaxis.

Acknowledgements : We thank Jeffrey Lipton, Arlene Redner, Caroline Fein-Levy, Jonathan Fish, Mark Atlas, Lawrence Wolfe, Sandra Cohen who treated these patients and implemented primary thromboprophylaxis in this cohort. We thank Jeffrey Lipton and Uma Athale for constructive critical comments.

Conflict of Interest : The authors of this manuscript a Susmita Sarangi, Marian Gaballah, Deirdre Nolfi-Donegan, Maria Battaglia, Seema Amin, John Amodio and Suchitra Acharya have no relevant conflicts of interest to report.

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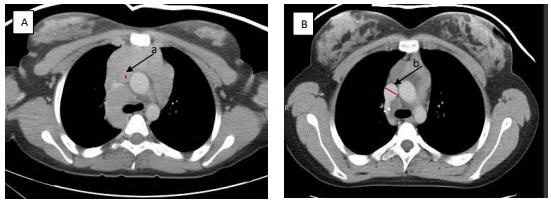
Legend List

FIGURE 1. Demonstration of vascular measurements. (A) Measurement of the narrowest luminal segment of the compressed SVC on initial pre-treatment contrast enhanced chest CT (a= 5 mm); (B) Measurement of the corresponding SVC segment on 6-month follow-up contrast enhanced chest CT, which demonstrates

normal, non-compressed luminal diameter (b= 18 mm). Percentage compressions were then calculated using the equation, [(b-a)/b]*100, where (a) represents the luminal diameter of the narrowest segment of the compressed vessel, and (b) represents the normal diameter of the previously compressed vascular segment on subsequent normal CT. Compression percentage in this case is 72%.



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