Risk factors for the occurrence of veno-occlusive disease in pediatric patients with solid tumors treated with Busulfan

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Introduction

High-dose chemotherapy with Busulfan Melphalan (BuMel) and peripheral stem cell autotransplantation became a major treatment in the late 20th century in the fight against certain paediatric cancers, foremost among them neuroblastoma and Ewing sarcoma. Recently, sinusoidal obstruction syndrome (SOS) has been refined, to distinguish probable, clinical and proven SOS. Literature has analyzed risk factors for Veno-occlusive disease (VOD) in stem cell transplantation: allogeneic transplantation, Busulfan, previous liver disease or previous radiotherapy. However, since BuMel has become a gold standard, VOD risk factors, especially for paediatric patients, have not been reassessed. The aim of this study is therefore to determine the risk factors for post-Busulfan VOD in a population of children and young adults treated for neuroblastoma or Ewing sarcoma.

Methods

We conducted a retrospective, single-center, case-control study to assess risk factors for the development of VOD in a population of children and young adults ≤ 25 years of age at diagnosis, with high-risk neuroblastoma or Ewing sarcoma, treated with high-dose BuMel chemotherapy. Risk factors were determined by analysis of the existing literature, by category: patient-related, biological factors, treatments received during high-dose chemotherapy, chemotherapy-related. SOS cases were defined as moderate or more, according to the new European Society for Blood and Marrow Transplantation (EBMT) definition, detected by systematic administration of Defibrotide. We calculated Odds-ratio, for each suspected risk factor.

Results

Between January 2015 and April 2023, we took into account 769 Busulfan administrations. Nine of the 48 patients (19%) developed VOD requiring treatment with Defibrotide (Figure 1). On average, more cases were recorded in patients under 5 years of age, with low weight or low body surface area for whom a chemotherapy regimen specific to weight categories between 9 and 16 kg was chosen. These patients received the lowest doses with the lowest administration rates. However, they received the highest relative doses, since the youngest patients received the highest dose/kg. This confirms the data found in the literature. No biological or pre-existing liver function abnormalities were detected in VOD patients. The only risk factor with a significant Odds ratio was concomitant total parenteral nutrition with lipid emulsion (OR = 5.09 [1.08 - 24.02]) (Figure 2 - Table 1). Neither Cotrimoxazole nor paracetamol administration were identified as risk factors. Not any protective factor has been found.

Conclusions

Our results suggest an increased risk with total parenteral nutrition with lipid emulsion, but further multi-center studies are required to confirm this risk.

Figure 1: Chronology of VOD events

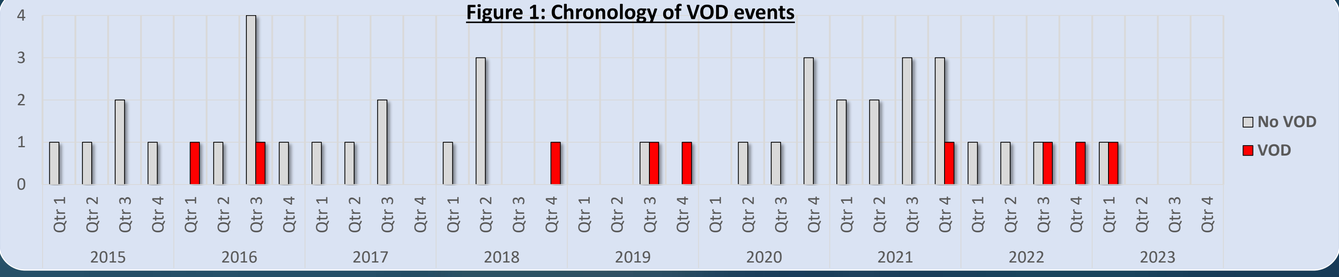

Figure 2: Forest plot of presumed risk factors

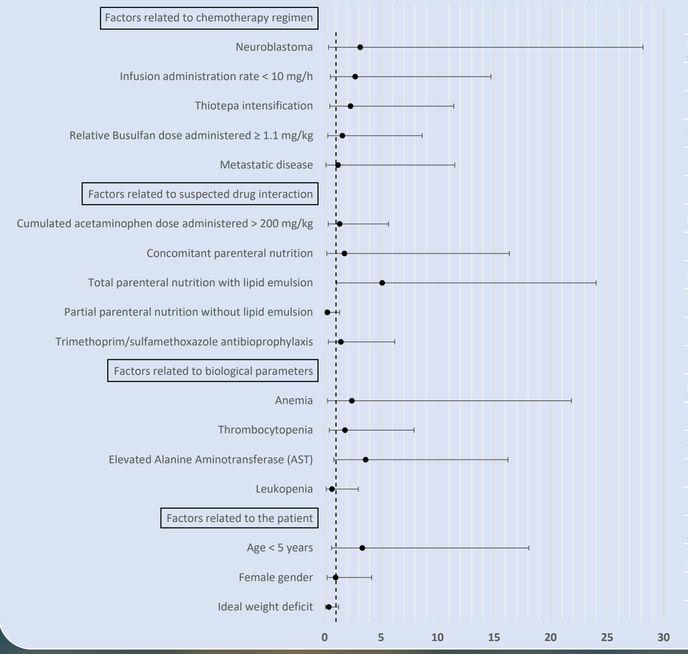

Table 1 : Odds ratios (95% confidence intervals) and P values

	Odds ratio, 95% CI	p-value
Factors related to chemotherapy regimen		
Neuroblastoma	3,14 [0.35 – 28.16]	0.306
Infusion administration rate < 10 mg/h	2,7 [0.50 – 14.72]	0.250
Thiotepa intensification	2,29 [0.46 – 11.43]	0.314
Relative Busulfan dose administered ≥ 1,1 mg/kg	1,56 [0.28 – 8.62]	0.613
Metastatic disease	1,18 [0.12- 11.51]	0.889
Factors related to suspected drug interaction		
Cumulated acetaminophen dose administered > 200 mg/kg	1,32 [0.31 – 5.65]	0.712
Concomitant parenteral nutrition	1,75 [0.19 – 16.34]	0.623
Total parenteral nutrition with lipid emulsion	**5,09 [1.08 – 24.02]**	**0.040**
Partial parenteral nutrition without lipid emulsion	0,24 [0.05 – 1.33]	0.103
Trimethoprim/sulfamethoxazole antibioprophylaxis	1,43 [0.33 – 6.20]	0.634
Factors related to biological parameters		
Anemia	2,4 [0.26 – 21.84]	0.437
Thrombocytopenia	1,8 [0.41 – 7.91]	0.436
Elevated Alanine Aminotransferase (AST)	3,63 [0.81 – 16.22]	0.092
Leukopenia	0,65 [0.14 – 2.97]	0.576
Factors related to the patient		
Age < 5 years	3,33 [0.61 – 18.06]	0.164
Female gender	0,97 [0.22 – 4.16]	0.963
Ideal weight deficit	0,36 [0.08 – 1.56]	0.171

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