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Review Article

Tolerability and Safety of Vincristine, Ifosfamide, Doxorubicin and Etoposide in Adolescent and Young Adult Patients with Ewing Sarcoma

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Abstract

Vincristine, ifosfamide, doxorubicin and etoposide (VIDE) is an intensive multiagent induction chemotherapy regimen used in the treatment of Ewing and other sarcoma, most often in children and younger adolescents. Its safety and tolerability in Adolescent and Young Adult (AYA) patients is not well documented. VIDE in this setting is novel, with only two Australian non-paediatric institutions adopting its use. This study aims to describe the experience of treating AYA sarcoma patients with VIDE at one of these two institutions, including an assessment of treatment-related adverse effects. Data from all sarcoma patients treated at Royal Prince Alfred Hospital and subsequently Chris O'Brien Lifehouse from 2013 to 2017 were analysed retrospectively. Assessment of VIDE administration, toxicity, and hospital length of stay was made from review of prescribing charts, medical records, and pathology results during treatment. Over this period, 13 patients aged 16 to 43 were treated with 74 cycles of VIDE. The most common toxicities were neutropenia (42%), anaemia (24%) and febrile neutropenia (41%). Dose modification occurred in 64% of cycles. No treatment-related deaths occurred. Even in patients subsequently admitted with febrile neutropenia, median total length of inpatient stay per cycle was 7 nights. VIDE chemotherapy in the AYA population is associated with frequent haematologic adverse events but acceptable tolerability and safety. Our experience demonstrates the feasibility of treating patients with VIDE in an adult oncology institution.

Introduction

Ewing sarcoma is a malignancy of bone and soft tissue arising predominantly in the second decade of life [1]. Treatment of Ewing sarcoma is multimodal, involving intensive multiagent induction chemotherapy, local therapy with surgery and/or radiotherapy, followed by consolidation chemotherapy. Up to 70% of patients with localised disease have long-term disease-free survival following this treatment, with overall survival upwards of 80% [2].

Intensive multiagent induction chemotherapy with six cycles of combination vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) is a standard induction regimen recommended in international guidelines [3,4], as described by the European Ewing tumour Working Initiative of National Groups 1999 (Euro-EWING 99) protocol and subsequently incorporated into the Ewing 2008 protocol. Published safety assessment of VIDE from 851 patients (74% aged ≤ 18 years) enrolled in the Euro-EWING 99 trial noted a high rate of adverse events including (with/without G-CSF) febrile neutropenia (61%/66%) and infection (55%/61%), rare renal and cardiac toxicity, and 9 deaths (1%) during treatment [5]. Dose modification was required in 21% of cycles. Only 26% of patients in the Euro-EWING 99 trial were aged greater than 18 years and there is limited published experience in older patients.

The use of VIDE chemotherapy is novel in Australian non-paediatric institutions, with only two adult centres adopting the regimen for the treatment of Ewing and other sarcoma. Barriers to utilising VIDE chemotherapy for older patients include reluctance to treat adult patients with protocols that require inpatient admission and concerns regarding overwhelming toxicity following an intensive regimen conceived for children and adolescents. This study aims to describe the tolerability and safety of delivering VIDE chemotherapy to Adolescent and Young Adult (AYA) patients with Ewing sarcoma in an adult institution, including an assessment of treatment-related adverse events in this population.

Materials and Methods

Consecutive patients receiving VIDE chemotherapy administered at Royal Prince Alfred Hospital and Chris O'Brien Lifehouse in Sydney, Australia from January 2013 to December 2017 were identified on retrospective chart review. Approval to conduct this research was obtained from

the local Human Research Ethics Committee (HREC) and a waiver of consent was granted given its retrospective nature.

Demographic information and toxicity were identified by reviewing the medical record of patients during treatment. Pathology results collected for monitoring in routine clinical practice were also reviewed. Toxicity was assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [6] and recorded if grade was 3 or greater. These included haemoglobin level, white cell, neutrophil and platelet count, creatinine level, estimated glomerular filtration rate, infection, stomatitis, vomiting, haematuria, neurotoxicity, cardiotoxicity and a free text area for other toxicities. Chemotherapy treatment delay and dose reduction was documented from review of prescribing charts. Data were collected by a single investigator into a standardized data abstraction form.

VIDE chemotherapy was given according to the Ewing 2008 protocol [5] as follows: vincristine 1.5mg/m^2/day (capped at 2mg) on day 1, ifosfamide 3000mg/m^2/day on days 1-3, doxorubicin 20mg/m^2/day on days 1-3 and etoposide 150mg/m^2/day on days 1-3. Supportive therapy included Mesna 1000mg/m^2 intravenous push on day 1 then 3000mg/m^2/day with adequate hydration of 2-3L/m^2/day on days 1-3 for urothelial protection and pegfilgrastim 6mg on day 4. Cardiac assessment with transthoracic echocardiogram or gated heart pool scan was performed at baseline and after 300-360mg/m^2 of doxorubicin to assess for cardiotoxicity. If dose reduction for toxicity was indicated, 20% reduction in etoposide occurred in preference to dose reductions of other drugs.

Results

We identified 13 patients treated with VIDE chemotherapy. Table 1 describes baseline patient and tumour characteristics. The median age was 21 (range 16 to 43) years. A total of 74 cycles of VIDE chemotherapy were administered (median 6, range 3 to 6). Of these, 11 patients completed all six cycles, 1 patient had emergency initial treatment with an alternative regimen then completed 5 cycles of VIDE, and 1 patient completed 3 cycles. The median length of stay for each cycle of inpatient chemotherapy was 3 nights (range 3 to 11). Dose modification occurred in 47 cycles (64%): initiated in cycle 2 for 8 patients, cycle 3 for 2 patients, cycle 5 for 1 patient, and not required for 2 patients. Without exception, dose modification consisted of 20% reduction in etoposide only, introduced after the first episode of febrile neutropenia and maintained for subsequent cycles. No dose reduction of other drugs occurred and there were no treatment delays.

Table 1: Patient demographics.

Patient characteristic		Frequency (N=13)
Age	Median (range)	21 (16 to 43)
	16-18	5
	19-29	6
	30-49	2
Sex	Male	6
	Female	7
Pathology	Ewing sarcoma	12
	Mesenchymal chondrosarcoma	1
Primary site	Upper limb	4
	Lower limb	5
	Spine or sacrum	1
	Other	3
Extent of disease	Localised	9
	Metastatic	4

Table 2: Observed grade 3/4 adverse events compared with the published safety assessment.

Grade 3/4 event	Number of cycles complicated (N=74)		VIDE safety assessment (N=4746) [5]
Neutropenia	31	42%	90%
Neutropenic fever	30	40%	61%
Anaemia	18	24%	57%
Thrombocytopenia	24	32%	62%
Stomatitis	1	1%	12%
Vomiting	0	0%	5%
Cystitis	0	0%	1%
Renal impairment	2	3%	0%
Cardiotoxicity	0	0%	0%
Neurotoxicity	0	0%	1%

Table 2 shows observed grade 3/4 adverse events. The majority were haematological in nature, including neutropenia (31 cycles, 42%), anaemia (18 cycles, 24%), thrombocytopenia (24 cycles, 32%) and febrile neutropenia (30 cycles, 41%). The median length of stay for febrile neutropenia was 4 nights (range 2 to 12). Other grade 3/4 toxicity was uncommon. No patient deaths occurred during treatment with VIDE chemotherapy.

Discussion

Our study demonstrates the feasibility of delivering intensive multiagent induction VIDE chemotherapy to an AYA population with Ewing sarcoma. We found frequent haematologic adverse events, but acceptable tolerability and safety.

Dose modification was required in 64% of cycles, however these were all with 20% reduction in etoposide with preserved doses of vincristine, ifosfamide, and doxorubicin. This compares to 13% of cycles having etoposide dose reduction and 21% having any dose reduction in the original Euro EWING 99 cohort [5].

Any grade 3/4 toxicities were observed following 36 cycles (49%) of VIDE. These were predominantly haematological in nature. Grade 3/4 neutropenia, anaemia and thrombocytopenia occurred significantly less than was seen in the original safety assessment [5]. This may relate to the timing of toxicity assessment: the original safety assessment examined for haematological toxicity on days 10-12 and 20-22 of each cycle while this study only had access to blood tests performed when clinically indicated during the course of chemotherapy delivery.

Another contributor to this difference in observed toxicity could be the older age of our patients: median age of 21 compared to 14.5 (estimated median) in the original paper [5]. Differences in toxicity

profile between AYA and paediatric patients treated for the same malignancy has been observed in the literature. A meta-analysis of 4,838 patients with osteosarcoma found that adolescents and adults had statistically significant less grade 3/4 toxicity than children [7]. The authors also noted higher toxicity in female patients, proposing that this could be due to puberty-related differences in patient size, metabolism, body composition and organ function. Similarly, toxicity data from a randomised controlled trial of 657 patients with rhabdomyosarcoma demonstrated that adolescents experienced less toxicity of any grade compared to patients aged less than 10 [8]. Again, differences in drug handling were thought responsible, with age-related pharmacokinetics of alkylating agent of particular importance.

Our patients experienced febrile neutropenia significantly less than what was observed in the original safety assessment [5]. Age-related pharmacokinetic differences may contribute to this. In contrast, in the general solid-organ oncology population at our centre Royal Prince Alfred Hospital over a similar time period, only 1.2% of 2,115 chemotherapy cycles were complicated with febrile neutropenia. This likely relates to a fundamental difference in chemotherapy dose intensity between these patients and those treated in general adult oncology. Chemotherapy in this latter population is typically delivered to older patients, in the outpatient setting, using less intensive single-agent or doublet regimens, and/or with palliative intent where significant symptomatic treatment-related toxicity is avoided. Despite this difference, there were no associated complications or deaths from febrile neutropenia in this study.

While VIDE chemotherapy is necessarily delivered as an inpatient and there is a high rate of subsequent admission for febrile neutropenia (41% of cycles), the overall healthcare burden was low. Even in cycles complicated by febrile neutropenia, the median total admitted time in hospital per cycle was 7 nights. The longest admitted time in hospital in a cycle was 18 nights for treatment and complications associated with one patient's third cycle of VIDE chemotherapy. This patient had a 6-day admission for initial chemotherapy complicated by fevers and gastrointestinal toxicity, then a 12-day admission for febrile neutropenia and grade 3 acute kidney injury. This patient, with mesenchymal chondrosarcoma, also demonstrated a lack of clinical or radiological tumour response and so received no further VIDE chemotherapy.

In conclusion, VIDE induction chemotherapy has significant but manageable toxicity in this study of adolescent and young adult patients. Supportive care and minor etoposide dose reduction allowed adequate dose intensity to be delivered. Overall, it was feasible to administer chemotherapy and treat subsequent complications in adult oncology institutions with a reasonable number of hospital bed days. Limitations to this study include its small sample size, retrospective nature and lack of mature follow-up. In particular, this impacts the assessment of patient-reported toxicity and longer-term complications such as cardiotoxicity, infertility or secondary malignancy.

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