ORIGINAL ARTICLE

Irinotecan and temozolomide in adults with recurrent sarcoma

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Abstract

Background: The combination of irinotecan and temozolomide (IT) has shown promising activity in children treated for recurrent sarcoma. This study investigates the safety and efficacy of IT chemotherapy in adults with recurrent sarcoma.

Materials/Methods: A retrospective review was performed on patients with recurrent sarcoma who received IT chemotherapy from 2009-2013. Outcomes of interest were time to treatment failure (TTF) and incidence of toxicity.

Results: IT chemotherapy was used in 24 patients including: Ewing's sarcoma (EWS, n=11, 46%); non-pleomorphic rhabdomyosarcoma (RMS, n=6, 25%); desmoplastic small round cell tumor (DSRCT, n=6, 25%); and leiomyosarcoma (n=1, 4%). Median TTF was 3.0 months (range 1.6-4.4). Partial responses were observed in 4 patients (17%), stable disease in 9 patients (37%) and progressive disease in 11 patients (46%). Grade 3 hematologic toxicity was as follows: anemia (n=5, 21%); neutropenia (n=3, 12%); and thrombocytopenia (n=1, 4%). Diarrhea was reported among 12 patients (50%) and 3 patients (12%) experienced severe diarrhea requiring hospitalization.

Conclusion: IT chemotherapy is tolerable with modest activity and represents a reasonable choice for adults with recurrent EWS or DSCRT. Further prospective studies aimed at this high risk population are warranted.

Keywords

Chemotherapy, Metastatic, Soft tissue tumors, Adults

1 Introduction

"Small round blue cell tumors" include, among others, non-pleomorphic rhabdomyosarcoma (RMS, embyronal or alveolar), Ewing sarcoma (EWS or primitive neuro-ectodermal tumors) and desmoplastic small round cell tumor (DSRCT) [1]. These sarcomas are characterized by sheets of small round blue cells on histological analysis and are associated with specific translocations involving FOXO1 (alveolar RMS) and EWSR1 (EWS and DSCRT) [2, 3]. In contrast to traditional adult soft tissue sarcomas, the small round blue cell tumors have a consistent, robust response to multi-agent systemic chemotherapy with anthracyclines and alkylating agents. However, adults with these sarcomas fare worse than children, especially at the time of relapse [4, 5]. The reasons for this observation remain unclear. Adults with

EWS are more likely to present with large pelvic or soft tissue tumors and with distant metastases compared to children; but, other factors may possibly play a role in the differences in age related outcomes [6, 7]. Relapse is therefore common, and novel treatment strategies are required.

Irinotecan-based chemotherapy combinations have shown some promise in the treatment of small round blue cell tumors. The combination of irinotecan and temozolomide (IT) has shown synergy in pre-clinical testing and tolerability in Phase 1 clinical trial testing and is effective in children with relapsed EWS with response rates of 56%-63% [6. 7]. Vincristine had also been added to irinotecan based regimens to treat children with relapsed RMS with response rates ranging from 26%-37% and is currently being studied as first-line therapy in children with newly diagnosed RMS through the Children's Oncology Group [8, 9].

Further data on the outcomes of adults treated with irinotecan-based chemotherapy is therefore needed. Here, we report on a single institution experience of irinotecan plus temozolomide in the treatment of adults with relapsed small round blue cell tumors.

2 Materials and methods

2.1 Patient selection

A retrospective chart review was completed for patients with relapsed sarcoma from Princess Margaret Cancer Centre/Mount Sinai Hospital receiving irinotecan and temozolomide between January 1st, 2009, and January 31st, 2013. Research ethics board approvals from both institutions were obtained for this study. Patients were included if they had received IT chemotherapy for recurrent/metastatic sarcoma, regardless of dose and schedule.

2.2 Data synthesis

Due to variability in irinotecan dosing, all patients were classified based on cumulative per cycle dose into three categories for analysis: 1) Low cumulative irinotecan dosing schedule which included patients who received irinotecan 20 mg/m^2 intravenously daily on Days 1-5 only; 2) High cumulative irinotecan dosing schedule including patients who received either irinotecan 50 mg/m^2 intravenously daily on Days 1-5 or irinotecan 20 mg/m^2 intravenously daily on Days 1-5 and 8-12; 3) Other irinotecan dosing schedules which included patients who received mixed irinotecan dosing regimens. Best response rates were evaluated according to reports of imaging studies (CT or MRI) that were carried out as part of standard of care. Response was classified as either: complete response (CR), partial response (PR), stable disease (SD) or progressive disease based on internal institutional radiology and investigator review. Radiographic response imaging was usually completed at the physician's discretion at 3-month intervals depending of clinical response. Laboratory-based toxicity information was obtained through hospital medical records and was retrospectively graded according to NCI-CTCAE [National Cancer Institute Common Terminology Criteria for Adverse events (Version 4)]. Clinical toxicity data were extracted from the medical record, but were not graded retrospectively.

2.3 Statistical analysis

Baseline characteristics and tumor response data were reported descriptively as medians and 95% confidence intervals (CI) were applicable. Kaplan-Meier analyses were used to estimate time to treatment failure (TTF) and overall survival.

3 Results

3.1 Patient demographics

Of a total of 24 patients reviewed, 11 (46%) were male. The median age at diagnosis was 27 years (range 13-59). Other patient characteristics are presented in Table 1. Sarcoma subtypes were EWS (n=11, 46%), non-pleomorphic RMS (n=6,

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25%), DSCRT (n=6, 25%), and leiomyosarcoma (n=1, 4%). The median time from original diagnosis to first relapse was 9.7 months (range 2.0 to 27.6). Gender was not equally distributed among the different sarcoma subtypes; males made up 5 of the 6 patients (83%) with DSCRT, 5 of the 11 patients (45%) with EWS, 1 of the 6 patients (17%) with RMS and none of the patients with leiomyosarcoma.

Table 1. Patient characteristics (n=24)

Patient characteristics	n (%)
Gender	
Male	11 (46%)
Female	13 (54%)
Age at baseline	
Median	28
Range	15-60
Sarcoma classification	
Ewing's sarcoma (EWS)*	11 (46%)
Rhabdomyosarcoma	6 (25%)
Desmoplastic small-round-cell tumor	6 (25%)
Leiomyosarcoma	1 (4%)
Previous Surgery	
Yes	17 (71%)
No	7 (29%)
Previous Radiation	
Yes	10 (42%)
No	14 (58%)
Previous 1st line chemotherapy	
VDC/IE	15 (63%)
VAC	5 (21%)
AI	1 (4%)
Other**	3 (12%)

Note. VDC/IE: Vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide; VAC: Vincristine, doxorubicin, cyclophosphamide; AI: Doxorubicin, ifosfamide
*EWS group includes one patient also classified as primitive neuroectodermal tumor (PNET)
**Other: single agent doxorubicin; (BEP) bleomycin, etoposide, cisplatin; and combination carboplatin, etoposide, and paclitaxel

3.2 IT treatment

All patients received oral temozolomide at 100 mg/m^2/day for 5 days every 21 days. The doses and schedule of irinotecan therapy varied, with many patients receiving a low dose (20 mg/m^2 on day 1-5 only) presented in Table 2. One patient also received irinotecan 10 mg/m^2 intravenously daily on Days 1-5 only, and two patients received a mixed regimen of irinotecan 20 mg/m^2 intravenously daily given on both Days 1-5 as well as Days 1-5 and 8-12. Fourteen patients (58%) of patients received IT as 1st line therapy after relapse. Only one patient received primary prophylactic granulocyte growth factor support. Patients were not given empiric cephalosporins to prevent diarrhea and were advised to take loperamide as needed. Reasons for discontinuation included disease progression (n=16, 67%), toxicity (n=3, 12%), physician preference (n=3, 12%) and patient preference (n=2, 8%). At the completion of data collection in December 2013, 17 patients (71%) had died and 7 patients (29%) were alive with disease.

3.3 Tumor response

Partial response was observed in 4 patients (17%), 9 patients (37%) exhibited stable disease (1 patient had stable disease for ≥ 6 months and 3 other patients had stable disease for ≥ 4 months) while 11 patients (46%) showed progressive disease as their best response. The partial responses were seen in EWS (n=3/11, 27%) and DSCRT (n=1/6, 17%). There were no responses seen in RMS or leiomyosarcoma. Stable disease was seen in EWS (n=3, 27%); RMS (n=2, 8%); and DSCRT (n=4, 25%).

Table 2. Irinotecan and Temozolomide dosing schedule

Treatment information	n (%)
Line of chemotherapy in the relapsed setting	
1st line	14 (58%)
2nd line	4 (17%)
3rd line	6 (25%)
Dosing schedule of irinotecan	
Low - (Irinotecan 20 mg/m^2 intravenously daily on Days 1-5 only)	11 (46%)
High - (Irinotecan 50 mg/m^2 intravenously daily on Days 1-5 or Irinotecan 20 mg/m^2 intravenously daily on Days 1-5 & Days 8-12*)	10 (42%)
Other**	3 (12%)
Dosing schedule of temozolomide	
100 mg/m^2 orally on Days 1-5	24 (100%)
Vincristine dose	
2 mg intravenously on Day 1	2 (8%)

*Published irinotecan and temozolomide regimen
**Irinotecan 10 mg/m^2 intravenously daily on Days 1-5 (n=1) or a combination of irinotecan regimens consisting of 20 mg/m^2 intravenously daily on both Days 1-5 and Days 1-5 & 8-12 (n=2)

3.4 Clinical outcomes

Results of the Cox Proportional Hazards analysis are shown in Table 3. Median TTF was 3.0 months (95% CI 1.6-4.4 months, see Figure 1A). The median OS was 8.3 months (95% CI 4.3-12.4 months, see Figure 1B).

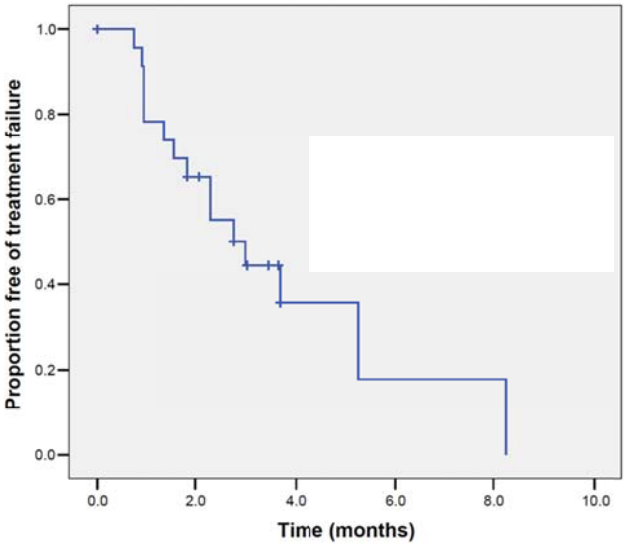

Figure 1A. Time to treatment failure of adult sarcoma patients treated with irinotecan and temozolomide chemotherapy (n=24)

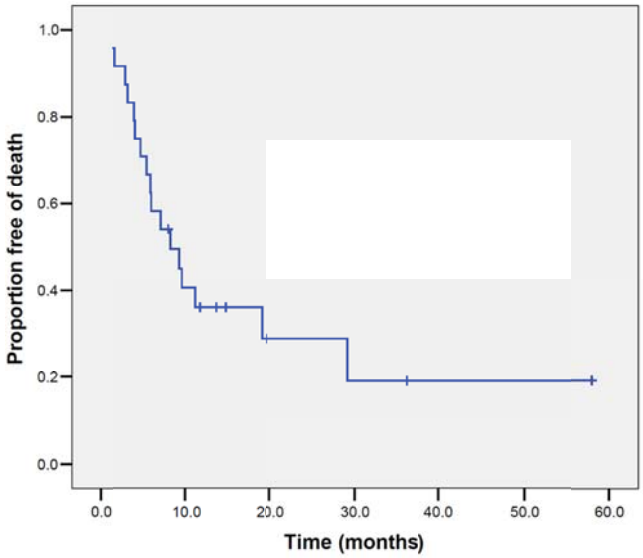

Figure 1B. Overall survival of adult sarcoma patients treated with irinotecan and temozolomide (n=24)

3.5 Toxicity

Data on toxicity is summarized in Table 3. Five patients (21%) experienced grade 3 or 4 anemia, for which one patient required a blood transfusion. One patient (4%) experienced grade 3 thrombocytopenia. Three patients (12%) experienced grade 3 or 4 neutropenia, leading to a treatment delay in two cases. Twelve patients (50%) experienced diarrhea of any grade. Three patients required hospitalization for severe diarrhea, all of these patients received a high dose schedule of irinotecan. Our study was not able to record which patients received loperamide or cefixime as to help treat diarrhea associated with irinotecan.

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Table 3. Toxicity observed by adults sarcoma patients treated with irinotecan and temozolomide chemotherapy (n=24)

Toxicity	n (%)
Anemia (Grade 3/4)	
Irinotecan dosing schedule	
Low	3 (13%)
High	1 (4%)
Other	1 (4%)
Total	5 (21%)
Thrombocytopenia (Grade 3/4)	
Irinotecan dosing schedule	
Low	1 (4%)
High	0 (0%)
Other	0 (0%)
Total	1 (4%)
Neutropenia (Grade 3/4)	
Irinotecan dosing schedule	
Low	1 (4%)
High	2 (8%)
Other	0 (0%)
Total	3 (13%)
Diarrhea (Any Grade)	
Irinotecan dosing schedule	
Low	4 (17%)
High	7 (29%)
Other	1 (4%)
Total	12 (50%)
Patients hospitalized due to diarrhea	
Irinotecan dosing schedule	
Low	0 (0%)
High	3 (13%)
Other	0 (0%)
Total	3 (13%)

Note. Low: Irinotecan 20 mg/m^2 intravenously daily on Days 1-5 only; High: Irinotecan 50 mg/m^2 intravenously daily on Days 1-5 or Irinotecan 20 mg/m^2 intravenously daily on Days 1-5 & Days 8-12 Other: Irinotecan 10 mg/m^2 intravenously daily on Days 1-5 or Irinotecan regimens that include a combination of 20 mg/m^2 intravenously daily on both Days 1-5 and Days 1-5 & 8-12

4 Discussion

Experience with the use of irinotecan and temozolomide in adult patients with relapsed sarcoma is limited. In our single institution experience, this regimen was tolerable but appeared to have inferior outcomes to those reported in children. The median TTF was 3.0 months, with no patients achieving a complete response. This modest outcome may reflect the variable dosing of irinotecan, as few adult patients received the traditional pediatric irinotecan dosing schedule. Inferior survival outcomes between adult and pediatric sarcoma patients with small round blue cell tumors have previously reported. The reason for poorer outcomes among adults is controversial, multifactorial and may potentially relate to underlying differences in tumor biology [4-7]. Additionally, our cohort of patients was heavily pre-treated and only 58% of patients received IT as 1st line therapy after relapse. Forty-two percent (42%) of patients received IT chemotherapy as a 2nd or later line of therapy in the relapsed setting.

The standard pediatric dosing of irinotecan has historically been 20 mg/m^2 intravenously daily on Days 1-5 and 8-12 administered every 3 weeks [10]. This low dose metronomic dosing schedule for irinotecan had been shown to increase the cumulative concentration of irinotecan's active metabolite SN-38 as compared to shorter high dose administration

schedules [11]. There is also pre-clinical evidence suggesting improved efficacy and less hematologic toxicity associated with a low dose protracted irinotecan dosing [12-14]. In addition, acute onset diarrhea is also less common in low dose regimens [15]. Nonetheless, due to patient convenience and ease of administration, short course high dose irinotecan has now evolved to be the preferred regimen among pediatric sarcoma patients. Our series reports significant variability in the dose scheduling of irinotecan. Only 25% of patients received the standard dosing of irinotecan and shorter dosing schedules were often employed to try and improve tolerability and for ease of administration.

Diarrhea was the most commonly experienced side effect observed in this study, especially among patients receiving a high dose irinotecan schedule. Pediatric protocols often employ the liberal use of prophylactic cephalosporin-based antibiotics to prevent irinotecan-associated diarrhea. Unfortunately, antibiotic prophylaxis to prevent diarrhea was not commonly used among adult patients in this study. Cefixime offers the ability to dose escalate oral irinotecan in children and should be considered in adult sarcoma patients [8]. Hematologic toxicity was minimal with this regimen despite very minimal use of granulocyte colony stimulating factor (G-CSF).

Vincristine was rarely administered in this series, although it is often used in combination with irinotecan and temozolomide in the pediatric setting [9, 16]. Combination irinotecan and vincristine has demonstrated a 70% response rate as compared to 42% in patients treated with irinotecan alone among untreated pediatric patients with RMS [17]. The proportion with progressive disease was 32% in patients given irinotecan alone and only 8% in patients given both irinotecan and vincristine. It is unclear whether a similar synergistic effect is present in other small round cell tumors, such as EWS or DSCRT.

This review gives an initial assessment of IT among adults patient with relapsed sarcoma. Our retrospective study is limited by diagnostic heterogeneity, small sample-size and the variable dosing schedules of irinotecan. Supportive care practices were also not standardized, specifically regarding use of cefixime, loperamide and G-CSF. Despite these limitations, our retrospective review is the first report of the use of IT chemotherapy among adults. This is of significance given the rarity of these cancers and the practical challenges on conducting clinical trials research in this setting.

In conclusion, IT chemotherapy appears to have modest activity in this limited review of adults with relapsed sarcoma. This study highlights the need for algorithms to guide the delivery of therapy even in the relapsed setting to ensure consistent attention to drug scheduling, dose modification and supportive care. Small round blue cell sarcomas remain a significant problem, as these patients are often young. Greater efforts are required to ensure equal opportunity to clinical trials sponsored by both pediatric and adult cooperative groups. We currently offer IT therapy to patients with first relapse small round cell sarcoma at our institution with an irinotecan schedule of 50 mg/m^2 intravenously daily on Days 1-5, with supportive care including cefixime and patient information sheets on the appropriate and early use of loperamide.

Conflict of interest

None of the authors have any conflict of interest to disclose.

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