HK J Paediatr (new series) 2012;**17**:223-229

Institutional Experience of Five-day Courses of Irinotecan as Palliative Chemotherapy in Chinese Patients with Refractory Neuroblastoma

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Abstract ***Purpose:*** To evaluate the efficacy, safety and quality of life of irinotecan in Chinese refractory neuroblastoma patients in affiliated hospitals of China Medical University. ***Patients and Methods:*** Seven patients received irinotecan at 40-50 mg/m^2/day administered as a 60-minute infusion for 5 consecutive days, every 3 weeks. Tumour response, toxicities and performance status were evaluated. ***Results:*** Stable disease was observed in 3 of 7 patients (42.9%). Most common grade 3-4 toxicities were myelosuppressive haematologic toxicities. Grade 1-2 nausea, vomiting, abdominal pain, or cramping and diarrhoea were the most common non-haematologic drug-related toxicities observed. Quality of life was improved in almost all patients. ***Conclusion:*** Irinotecan as a single agent was well tolerated and was a very safe regimen in Chinese patients. Although this regimen induced no objective response (CR+PR) in refractory neuroblastoma patients, the clinical benefit rate (CR+PR+SD) was 42.9%. This regimen could alleviate pain and to some extent improve the quality of life for heavily pretreated refractory Chinese neuroblastoma patients.

Key words Efficacy; Irinotecan; Neuroblastoma; Quality of life; Toxicity

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Received December 1, 2011

Introduction

Neuroblastoma is a neural crest derived paediatric malignancy that occur predominantly in early childhood. More than half of the patients with neuroblastoma have metastatic disease at diagnosis. Intensive combination of chemotherapy drugs including high dose myeloablative chemotherapy with peripheral blood stem cell rescue followed by 13-cis-retinoic acid has improved the prognosis of patients with advanced neuroblastoma.[1-5] However, in relapse and refractory cases, especially patients after stem cell transplantation, few treatment regimen could be selected to treat these patients due to drug resistance and bad performance status. Intensive chemotherapy sometimes results in severe therapy-related toxicity and decrease in performance status (PS) and quality of life (QOL).[1-7]

Irinotecan (IRN, CPT-11) is a semisynthetic water soluble analog of camptothecin which was first isolated from the Chinese tree *Camptotheca acuminata* and it is a prodrug that undergoes de-esterification to a much more potent topoisomerase I poison, SN-38. The clinical antitumour activity of IRN has been confirmed in a wide

variety of adult tumour types, including colorectal cancer, gastric cancer, lung cancer, refractory leukaemias and lymphomas, refractory gliomas, epithelial ovarian cancer or cervical cancer.[7-16]

Topoisomerase I inhibitor, topotecan and IRN represent promising new anticancer agents for the treatment of childhood cancer. IRN was shown to be highly effective both in vitro and in vivo in a variety of paediatric tumours such as neuroblastoma, rhabdomyosarcoma and central nervous system (CNS) tumours.[17,18] Different dose and schedules have been administered in clinical trials and case reports in paediatric population. Although Phase I and Phase II study in the US and Europe showed most of the recurrent, relapse or refractory neuroblastoma patients did not get objective response from IRN single agent treatment.[19,20] There has been cases of paediatric patients with neuroblastoma, who have been treated with irinotecan and got response. IRN has been reported to stabilise advanced neuroblastoma clinically and also markedly improve the quality of life of refractory and recurrent neuroblastoma patient for a significant time in Japan.[7,21]

In this report, we present the results of IRN given daily for 5 days every 3 weeks in refractory neuroblastoma according to the schedule recommended by Children's Oncology Group (COG). We design this study to determine whether protracted irinotecan as a single agent could be effective and tolerable in Chinese patients with refractory neuroblastoma and whether these patients could benefit from this treatment regimen.

Patients and Methods

1. Patients

Patients aged between 3 years and 22 years at the time of inclusion into the study with histologically confirmed neuroblastoma, which was refractory to standard treatments, were eligible to participate in the study. Other inclusion criteria included: measurable or evaluable primary and/or metastatic disease by imaging or bone marrow pathology; predicted life expectancy of ≥8 weeks; Karnofsky or Lansky performance status ≥50; adequate bone marrow function (absolute neutrophil count >1000 ul/L, platelets >80000/ul, haemoglobin >8 gm/dl, or patients with bone marrow metastasis and inadequate bone marrow function was supported by blood component infusion before treatment); bilirubin less than 1.5 mg/dl, ALT less than 3 x upper limit of normal; creatinine normal for age or glomerular filtration rate ≥70 ml/min/1.73 m^2; no uncontrolled infection; no concurrent anticancer therapy at least 3 weeks since prior chemotherapy; at least 8 weeks from radiotherapy of assessable lesions; and recovery from toxicity of prior therapy; the parents or patients gave written consent for the treatment after being informed of the rationale for the treatment, the known side effects of IRN, and the possibility of unforeseen life-threatening toxicities.

2. Treatment Schedule

IRN was supplied by Pfizer Inc. (China). IRN 40-50 mg/m^2/day was administered as a 60-minute intravenous infusion daily for 5 days every 21 days. 40 mg/m^2/day was administered in the heavily pretreated patient group (patients who have received >2 treatment regimen), and 50 mg/m^2/day were administered in the less-heavily pretreated patient group (patients who have received ≤2 treatment regimen). If the white blood cell counts at day 21 were less than $1.0x10^9$/L for neutrophils or less than $6x10^9$/L total, the next IRN cycle was delayed by 1 week and the dose was reduced by 20%. If there is no recovery at day 28, the treatment was terminated and the patient was withdrawn from the study unless a clear drug-related benefit for the patient like obvious alleviation of pain was shown. IRN treatment was continued until progression, unacceptable toxicities or patient's refusal.

Concomitant treatment included transfusion of blood, blood component like RBC or platelets and/or G-CSF when Grade 3 to 4 haematological toxicity was observed. Supportive care and loperamide were administered when IRN-induced diarrhoea happens and granisetron hydrochloride were administered to control nausea and vomiting.

Patient histories, physical examination and lab studies were obtained before treatment and then weekly throughout the courses of the study. Laboratory evaluation included electrolytes, blood urea nitrogen, creatinine, and liver function tests. Complete blood counts were obtained at least twice weekly throughout the courses of the study. Patients with measurable disease had appropriate radiographic or bone marrow pathological evaluations at baseline, after the second cycle of IRN treatment and every other cycles of IRN treatment to assess tumour response.

3. Treatment Assessment

During treatment, anti-tumour efficacy was assessed according to every two cycles and/or at the end of the treatment, then during follow-up, every month. The initial target lesions were measured by baseline method. Response was defined according to the International Neuroblastoma

Response Criteria (INRC).[22]

All eligible patients who received at least 5 days of IRN and whose disease was assessed at least once and response was confirmed, or who died as a result of disease-related causes before the first disease assessment were considered assessable for response. A complete response (CR) was defined as the complete resolution of all evidence of disease for at least 3 weeks. A partial response (PR) was defined as ≥50% reduction on the sum of the products of the two longest perpendicular diameters of all measurable tumours. A minimal response (MR) was a ≥25%, but ≤50% reduction in all measurable lesions, no evidence of progression of any lesion, and no evidence of new lesions. A stable disease (SD) was defined as a decrease in tumour size less than a MR but with no disease progression. Progressive disease (PD) was defined as a more than 25% increase in the measurable lesions or the appearance of the new lesions. We considered a CR or PR to be evidence of the activity of IRN in a particular patient, and classified these patients as having a response for study analysis.

Toxicities, graded according to the National Cancer Institute Common Toxicity Criteria (CTCAE) version 3.0 was assessed by clinical and biological examinations before each cycle (weekly within a cycle for haematological toxicity), and then at the end of treatment.

Karnofsky or Lansky performance status and face rating pain scale were used to evaluate quality of life preliminarily after the first course and before the second course of treatment.

4. Statistical Analysis

Objective response rate (ORR) (CR plus PR) were firstly considered as drug efficacy. Tumour response were to be confirmed by two evaluations to be considered. The secondary efficacy criteria were the duration of response, the time to progression (TTP), and the survival. The third efficacy criteria were the clinical benefit rate (CBR) (CR plus PR plus MR plus SD). The worst toxicity grade for each patient in each cycle of chemotherapy was used. The safety analysis was performed in all patients who received at least one dose of study drug. QOL were evaluated by performance status and pain scale after the first course and before the second course of treatment.

Results

1. Patient Characteristics

A total of 7 patients were recruited by hospitals of China Medical University into the study. And all the patients got baseline assessment and were eligible for analysis. Patient characteristics at baseline are described in Table 1.

The patients had a median age of 11 years of age (range, 3-22 years) and majority of them were male (5/7) and had stage IV disease (5/7) at diagnosis. All patients presented with metastatic disease at study entry. The median time from diagnosis to the first IRN infusion was 43 months (range 7-132 months). Most patients were at first relapse (5/7), one patient was at second relapse (1/7) and one patient had got recurrent disease and have three surgeries and still had a refractory tumour after 11 years of first diagnosis. All patients had received prior chemotherapy (mainly vinca-alkaloids compounds, platinum, anthracyclines, etoposide and cyclophosphamide. One patient had been treated with topotecan combined with cyclophosphamide for 2 cycles. One patient received prior myeloablative chemotherapy with autologous peripheral blood stem cell transplantation (PBSCT) followed by oral 13-cis retinoic acid treatment.

2. Efficacy

A total of 21 cycles were administered to 7 patients, with a median number of 3 cycles per patient (range, 1-5 cycles). All the patients did not need any dose reduction during the study and 3 patients got treatment delay to 28 days for 5 cycles due to haematological toxicity. The reasons for treatment discontinuation were progressive disease (3/7), disease related death (3/7), no further expected benefit (1/7). All the 7 patients were assessible for response. Overall, no objective response was observed during the study. Stable disease was noted in 42.9% patients (3/7) and the clinical benefit rate was 42.9% (3/7). Four patients are still alive till the summary of the clinical data (Table 2).

3. Toxicity

Myelosuppression and gastrointestinal disorders were the main toxicities. Grade 3-4 neutropenia occurred in 28.6% patients (2/7), and in 19.0% cycles (5/21) and a median recovery gaining at least at a grade 2 occurring within 4 days with G-CSF treatment. No patient experienced febrile neutropenia. Grade 3-4 anaemia occurred in 28.6% patients (2/7), and in 9.5% cycles (2/21). Grade 3 or 4 thrombocytopenia occurred in 14.2% (1/7) patients in 4.8% cycles (1/21). What need to be mentioned is that one patient who had bone marrow metastasis got even better whole blood count result after one cycle of treatment. Transfusion of blood and blood component was administered in patients with grade 3 or 4 haematological toxicities. No severe and irreversible

abnormalities for hepatic or renal function were detected even in patients with liver metastasis. Mild and manageable vomiting, nausea, abdominal pain or cramping, diarrhoea were the common non haematological drug-related toxicities observed. Although severe delayed diarrhoea was a common side effect caused by irinotecan due to chemotherapy induced mucositis,[7] no grade 3-4 diarrhoea were observed in this group. We did not detect UGT1A1 gene polymorphism which has been reported to be associated with IRN induced diarrhoea in this cohort of patients.[23] Loperamide Hydrochloride and supportive care were administered as anti-diarrhoea treatment in 2 patient for 2 cycles. Concurrent cephalosporin was not used to control diarrhoea. Granisetron Hydrochloride were administered to control nausea and vomiting. No treatment-related death occurred during the study (Table 3).

4.Quality of Life

As we mentioned before, only Karnofsky or Lansky PS ≥50 were eligible for this study, almost all the patients got obvious improvement of PS after one course of treatment. Patient 4 with lower limb paralysis due to multiple metastasis of lumbar vertebrae could stand up and walk by himself after IRN treatment. Alleviation of pain was the very exciting phenomenon observed in most of patients. Alleviation of bone pain was the main cause of improvement of quality of life observed (Tables 4 & 5).

Discussion

Studies of topoisomerase I inhibitors were started and developed in paediatrics in 1990s. Topotecan was the first camptothecin analogue which under-went evaluation in children. Topotecan, as a single agent or in combination with other drugs is currently in clinical trials for rhabdomyosarcoma, neuroblastoma and Wilm's tumour.[24-26] IRN has been evaluated in phase II clinical trial

Table 1 Patient characteristics at baseline (N=7)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years at diagnosis)	11	3	11	3	2	4	20
Age of years at inclusion	13	5	14	14	3	9	22
Sex	M	M	F	M	F	M	M
Stage of disease	IV	IV	IV	IV	IV	IV	IV
First line of chemotherapy drugs	Cyclo,VCR, ADM,VP-16, DDP	Cyclo,VCR, ADM,VP-16, DDP	Cyclo,VCR, ADM,VP-16, DDP	Cyclo,VCR, ADM,VP-16, DDP	Cyclo,VCR, ADM,VP-16, DDP	Cyclo,VCR, ADM,VP-16, DDP	Cyclo,VCR, ADM,VP-16, DDP
Remission status after first line treatment	PR	PR	PR	PR	PR	PR	PR
Number of courses of chemotherapy	12	12	20	40	8	30	12
Radiotherapy	N	N	Y	Y	N	N	N
Surgery	N	Y	Y	Y	Y	Y	Y
Autologous BMT	N	N	N	N	N	Y	N
Relapse status	Distant disease	Distant disease and regional relapse	Distant disease	Distant disease	Distant disease and regional relapse	Distant disease	Distant disease and regional relapse
Main symptoms caused by relapsed disease	Anaemia and haemorrhage	No symptom	Anaemia and bone pain	Paralysis and severe bone pain	Abdominal pain and mass and bone pain	Anaemia black eye orbit and bone pain	No symptom
Performance status (Karnofsky or Lansky)	**60**	**80**	**50**	**50**	**60**	**60**	**100**

M: male; F: female; Cyclo: cyclophosphamide; VCR: vincristine, ADM: adriamycin; VP-16: etoposide, DDP: cisplatin; PR: partial reponse; BMT: bone marrow transplantation; N: no; Y: yes

using different schedules in US and Europe. In the US, IRN was administered as a protracted or a weekly schedule, which showed efficacy in newly diagnosed metastatic rhabdomyosarcoma and in high-risk malignant brain tumours. In Europe, irinotecan was administered as a 3-week schedule and showed modest antitumour activity in recurrent rhabdomyosarcoma (ORR=11.4%) and recurrent medulloblastoma (ORR=17.6%).[19,20,27,28] In Japan, partial response has been reported in patients of neuroblastoma, rhabdomyosarcoma, nephroblastoma, undifferentiated sarcoma and leiomyosarcoma treated with IRN.[21]

Table 2 Efficacy results of irinotecan (N=7)

	No. of patients (%)
Complete response	0 (0)
Partial response	0 (0)
Minimal response or stable disease	3 (42.9)
Progressive disease	4 (57.1)
Objective response rate	0 (0)
Clinical response rate	3 (42.9)

Table 3 Grade 3-4 Toxicities of irinotecan

	No. of patients (N=7)(%)	No. of cycles (N=21)(%)
Haematological toxicities		
neutropenia	2/7 (28.6)	4/21 (19.0)
anaemia	2/7 (28.6)	2/21 (9.5)
thrombocytopenia	1/7 (14.2)	1/21 (4.8)
Non-haematological toxicities	0/7 (0)	0 (0)
Treatment-related death	0/7 (0)	0 (0)

Table 4 Karnofsky or Lansky performance status

	No. of patients (BT) (%)	No. of patients (AT) (%)
80-100	2/7 (28.6)	3/7 (42.8)
60-70	3/7 (42.8)	4/7 (57.1)
50	2/7 (28.6)	0 (0)

BT: before treatment; AT: after treatment

Table 5 Face rating pain scale

	No. of patients (BT) (%)	No. of patients (AT) (%)
6-10	2/7 (28.6)	0/7 (0)
2-5	2/7 (28.6)	2/7 (28.6)
0-1	3/7 (42.8)	5 (71.4)

BT: before treatment; AT: after treatment

The anti-tumour activity of IRN in neuroblastoma has been reported in phase I clinical trials and case reports using different schedules of IRN. Totally 6 partial response and 12 stable disease have been observed in 56 neuroblastoma patients.[19] In phase II study, COG observed only 1 partial response in 18 patients of neuroblastoma treated with IRN 50 mg/m^2/day for 5 consecutive days, every 3 weeks.[19] Société Française d'Oncologie Pédiatrique (SFOP) and United Kingdom Children Cancer Study Group (UKCCSG) observed no objective response in 37 children with relapsed or refractory neuroblastoma by administration of IRN at 600 mg/m^2 as a 60-min infusion, every 3 weeks.[20] Kushner's group administered IRN according to COG's dose and schedule as palliative therapy for patients with neuroblastoma and showed that in heavily treated patients, the regimen studied was well tolerated, allowed patients to continue most normal life activities, and produced anti-neuroblastoma effects.[29] Shitara and colleagues conducted a phase II study with 180 mg/m^2/day for 3 consecutive days, repeated once after 25 days off in 7 neuroblastoma patients and there was one patient with partial response and four with stable disease.[21] Osone reported 2 cases of stage 4 neuroblastoma with poor PS that received 20 mg/m^2/day of irinotecan infused intravenously over 1 hour for 5 consecutive days every 21 days as palliative chemotherapy and showed that low-dose IRN not only stabilised the disease, but also markedly improved the QOL for a significant time.[7] Inagaki reported that a 1-year-old patient with a stage 3 neuroblastoma diagnosed through mass screening experienced prolonged CR after IRN treatment.[30] One complete remission with single agent IRN was observed out of 15 neuroblastoma patients in a randomised trial.[31]

In our study, IRN was administered at 40-50 mg/m^2/day administered as a 60-minute infusion for 5 consecutive days, every 3 weeks in Chinese population mainly according to COG's regimen. We achieved stable disease in 3 patients out of 7 refractory neuroblastoma patients with no severe and irreversible toxicity and improvement of quality of life in most of these patients. The dose and schedule we used is feasible with poor bone marrow reserve which has been verified by Kushner and colleagues too. Overall, IRN as a single agent in refractory neuroblastoma whatever the schedule have little response but is well-tolerated and could to some extent improve quality of life of patients. Quality of life was a major issue in choosing this regimen for patients whose disease was resistant to standard anti-neuroblastoma therapies.

There have been reported of preclinical testing and clinical trials of IRN in combination with other

chemotherapy drugs in paediatric patients. Phase I and Phase II trials of different formulation of IRN and temozolomide for children with relapsed high-risk neuroblastoma and other refractory solid tumours have been reported and preliminary data have shown some efficacy of this combination in neuroblastoma.[31-36] In conclusion, all the data of IRN as a single agent or combination with other chemotherapy drugs in paediatric patients suggest a basis for more evaluation of IRN in combination with other chemotherapy in childhood cancer.

Acknowledgement

Supported Partially by National Natural Science Foundation of China (Grants No.30900384, 81041073); Liaoning Science and Technology Planning Foundation (Grants No.2008225008-11,2010225001).

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