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Abstract

The objective of the present study was to evaluate the efficacy and safety of regorafenib in comparison with dinutuximab with chemotherapy in Chinese children with advanced neuroblastoma. The patients aged less than 16 years who were histologically diagnosed with advanced neuroblastoma were enrolled and randomized to receive either regorafenib plus best supportive care or dinutuximab plus chemotherapy plus best supportive care in a 1:1 ratio. The tumor response assessment was made in accordance with modified international neuroblastoma response criteria. Adverse events were also assessed. Regorafenib showed prolonged overall survival and progression-free survival than who received dinutuximab plus chemotherapy (overall survival: median 32.3 months versus 27.2 months; hazard ratio = 0.45; 95% CI 0.11-0.13, $p < 0.001$; progression-free survival: stratified hazard ratio = 0.48; 95% CI 0.11-0.14; $p < 0.01$). Moreover, the overall response rate was greater in patients treated with regorafenib as compared to dinutuximab group. Regorafenib appears efficacious and has a manageable safety profile in Chinese children with advanced neuroblastoma.

Introduction

Neuroblastoma in children is one of most commonly diagnosed cancer and the leading cause of cancer mortality in the world, accounting for more than 15%. The incidence and mortality of childhood neuroblastoma have increased steadily (Kushner, 2004; Boubaker and Bischof, 2003; Hiorns and Owens, 2001; Schwab et al., 2003).

The molecularly targeted therapies are being studied, and the combination of targeted agents with chemotherapy may be advantageous. Irinotecan and temozolomide can be safely administered to the patient with relapsed or refractory neuroblastoma. The monoclonal antibody as monotherapy or combination with the chemotherapy is the standard therapy for the advanced neuroblastoma. The chemotherapeutic agents common-

ly used in clinical practice include irinotecan or temozolomide, and their combination regimens. In recent years, combination of temsirolimus and dinutuximab agents to chemotherapy regimens, either in the first or second line for the patient with neuroblastoma, have significantly improved overall survival, progression-free survival, and response rate (Grothey et al., 2013; Cao et al., 2016; Li et al., 2018; Xu et al., 2017). However, the majority of patients still developed resistance to the standard treatment (Xu et al., 2017; Motzer et al., 2007).

Regorafenib is the first small-molecule multi-kinase inhibitor of VEGFR offers survival benefits in patient with solid cancer who has grown after first/second-line of standard therapies (Kamba and McDonald, 2007). Currently, a pharmacological study shows that regorafenib is efficacious in suppressing the tumor



growth in preclinical model. However, no clinical studies have been conducted to evaluate the efficacy and safety of regorafenib in children with neuroblastoma.

Regorafenib is selective against VEGFR1, 2, and 3. It shows an acceptable safety profile and evidence of anti-tumor activity in patient with advanced solid tumor in several oncology clinical studies (Lacouture et al., 2008; Kamba and McDonald, 2007). In the present study, we hypothesized that regorafenib demonstrated a significant and clinically benefit in terms of overall survival in Chinese children with neuroblastoma. Efficacy of regorafenib was compared to dinutuximab.

Materials and Methods

Study design and participants

This is a preliminary study comparing regorafenib versus dinutuximab in Chinese children with advanced neuroblastoma. The overall safety profile of regorafenib was assessed. In patients who had Karnofsky/Lansky scores less than or equal to 50%, with age less than 16 years who histologically and/or cytological were diagnosed with advanced neuroblastoma, with increased urine level of catecholamine were enrolled. The patient with insufficient response after four cycles of more than 2 chemotherapeutic agents, that included alkylating agents and platinum-containing chemotherapeutic agents were also eligible for the enrollment. Patients who had previously received any VEGFR inhibitors or had other uncontrolled medical disorders were excluded. The patients who were previously treated with anti-epidermal growth factor receptor or VEGF agents were allowed but were not mandatory.

In this study, a total of 65 patients were screened, and 60 patients were randomized to receive either regorafenib plus best supportive care (n=30) or dinutuximab plus chemotherapy (irinotecan and temozolomide) plus best supportive care (n=30) between January 2016 and December 2017.

Study treatment

In this study, the eligible participants were randomized to receive either regorafenib plus best supportive care or dinutuximab plus chemotherapy (irinotecan and temozolomide) plus best supportive care in a 1:1 ratio. The participants of the regorafenib group received regorafenib 160 mg taken orally once daily for the first 21 days of each 28-day cycle. Dinutuximab (25 mg per day) was administered as intravenous infusion along with oral temozolomide (100 mg per day) and irinotecan (50 mg per day) intravenously. All randomized patients received either regorafenib plus best supportive care or dinutuximab plus chemotherapy (irinotecan and temozolomide) plus best supportive care until discontinuation due to intolerable toxicity or tumor progression or patient and investigator decision to stop

the treatment or death.

Efficacy and safety assessment

Tumor response assessment was conducted every 8 weeks until the disease progression in accordance with the INR Criteria (Modified International Neuroblastoma Response Criteria), using computed tomography and/or magnetic resonance imaging evaluations to assess the overall response. The patients with partial or complete response were defined as responders. The number (percentage) of patients with partial response, complete response, stable disease and progressive disease were identified as per the standard definition. The overall survival and progression-free survival were calculated. Adverse events were recorded using CTCAE version 4.03, and recorded throughout the study period. Standard laboratory tests were performed at each visit.

Statistical analysis

Since, the present study designed as a preliminary or pilot study, thus, no official sample size calculation was performed. To assess the efficacy of treatment, progression-free survival and overall survival were compared between both the treatment groups using a log-rank test, and hazard ratio (with 95% confidence interval) was calculated. Safety data were summarized by treatment group and presented descriptively.

Results

Patient characteristics ad dose exposure

The majority of patients in both groups had Karnofsky performance status of less than 50%. In general, both groups were similar in terms of baseline demography and disease characteristics (Table I). The patients in the regorafenib group were treated for a longer period than those in the dinutuximab with chemotherapy group, with a mean treatment duration of 3.2 months versus 2.2 months, respectively. The patients in the regorafenib group received more treatment cycles than those in the dinutuximab with chemotherapy group, with a mean (SD) treatment cycle of 6.1 (1.18) versus 3.9 (2.11).

Efficacy

The patients who were treated with regorafenib showed prolonged overall survival compared to those who received dinutuximab plus chemotherapy (median 32.30 months versus 27.17 months; hazard ratio = 0.45; 95% CI 0.11-0.13, $p < 0.001$). Also, progression-free survival was significantly prolonged for the patients who were treated with regorafenib compared with patients who received dinutuximab with chemotherapy (stratified hazard ratio = 0.48; 95% CI 0.11-0.14; $p < 0.001$). Moreover, the overall response rate was greater in patients treated with regorafenib as compared to dinutuximab with chemotherapy (Table II).

Table I		
Characteristics of the patients		
Characteristics	Best supportive care plus	
	Regorafenib	Dinutuximab plus chemotherapy
<i>Age</i>		
<10 years (n)	16	13
≥10 years (n)	14	17
<i>Gender</i>		
Male (n)	20	11
Female (n)	10	19
<i>Ethnicity</i>		
Han (Chinese)	28	27
Not Han (Chinese)	2	3
<i>Karnofsky performance status</i>		
≤50%	26	25
>50%	4	5
<i>Site of tumor</i>		
Primary	22	19
Metastatic	8	11
<i>Mutations in the Kirsten ras gene status</i>		
Wild type	29	28
Mutant	1	2
Prior use of anti-VEGF treatment	16	18
Prior use of anti-EGFR treatment	15	13
Liver metastasis	0	0
n=30 in each group; Abbreviations: EGFR= epidermal growth factor receptor; VEGF= vascular endothelial growth factor		

Safety and tolerability

In regorafenib group, the most common treatment-related adverse events of all grades were hypertension, palmar-plantar erythrodysesthesia syndrome hand-foot-skin-reaction, and proteinuria (Table III). The most common treatment-related grade ≥3 AEs were hypertension, hand-foot-skin-reaction, and proteinuria.

Discussion

The overall efficacy and safety profile of regorafenib in this study was consistent with the known efficacy and safety profile of regorafenib in other cancer treatment. Moreover, the safety and efficacy profile of regorafenib was mostly similar with those of other small molecular multi-target inhibitors which also antagonizing VEGFR (Motzer et al., 2007; Escudier et al., 2007; Motzer et al., 2013; Motzer et al., 2009; Escudier et al., 2007; Kamba and McDonald, 2007; Lacouture et al., 2008). In general, regorafenib treatment was well-tolerated in Chinese children with advanced neuroblastoma. In the study, the most common treatment-related adverse event occurred in neuroblastoma patients treated with regorafenib were hypertension, hand-foot-skin-reaction, proteinuria, and hemorrhage. The most common treatment-related grade ≥3 adverse events were hypertension, hand-foot-skin-reaction, and proteinuria. Hypertension was the most commonly reported treatment-related adverse event which is expected safety concern with various anti-VEGF/VEGFR agents (Motzer et al., 2013; Motzer et al., 2009; Escudier et al., 2007; Kamba and McDonald, 2007; Lacouture et al., 2008). This was possibly due to decrease release of nitric oxide, which is essential for maintaining blood pressure (Kamba and McDonald, 2007; Lacouture et al., 2008). Hand-foot-skin-reaction and proteinuria occurred after treatment is

Table II		
Efficacy comparison of regorafenib vs dinutuximab plus chemotherapy		
Variables	Best supportive care plus	
	Regorafenib (n=30)	Dinutuximab plus chemotherapy (n=30)
<i>Overall survival</i>		
Median in months (95% CI)	32.3 (8.1-10.5)	27.2 (5.7-8.1)
Stratified hazard ratio (95% CI), p value	0.45 (0.11-0.13), p<0.001	
<i>Progression-free survival</i>		
Median in months (95% CI)	8.8 (4.7-10.6)	5.1 (2.8-8.8)
Stratified hazard ratio (95% CI), p value	0.48 (0.11-0.14), p<0.001	
<i>Overall response (n)</i>		
Complete response	2	1
Partial response	13	9
Stable disease	12	15
Progressive disease	3	5

Table III

Comparison of treatment-related adverse events in children with neuroblastoma (safety population)		
Best supportive care plus		
Adverse events	Regorafenib	Dinutuximab plus chemotherapy
Hypertension	13	11
Hand-foot skin reaction	14	12
Rash	12	9
Proteinuria	19	18
Occult blood positive	8	12
Epistaxis	9	19
Hematuria	12	12
Hypothyroidism	20	19

n=30 in each group; No Grade 5 treatment-related treatment-emergent adverse event occurred at an overall rate $\geq 5\%$

possibly due to the inhibition of VEGF receptors (Kamba and McDonald, 2007; Lacouture et al., 2008). No severe and fatal treatment-related toxicities have been reported in patients treated with regorafenib. However, it has been observed with other small molecule VEGFR inhibitors (Lacouture et al., 2008). Overall, regorafenib appeared efficacious and have a manageable safety profile and well tolerated in the treatment population. The majority of adverse events were associated with the mechanism of action of the regorafenib, and consistent with those of its therapeutic class. Also, regorafenib demonstrated a significant and clinically benefit in terms of overall survival and progression-free survival as compared with dinutuximab with chemotherapy in Chinese children with advanced neuroblastoma.

Conclusion

Regorafenib appears efficacious and has a manageable safety profile in Chinese children with advanced neuroblastoma.

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Ethical Issue

Written informed consent was taken from each patient and ethics committee approval was obtained from the Institutional Ethics Committee of Dezhou People's Hospital.

Conflict of Interest

Authors declare no conflict of interest

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