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BRIEF COMMUNICATION

Reported outcomes of children with newly diagnosed high-grade gliomas treated with nimotuzumab and irinotecan

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Abstract
Purpose The outcome of children with high-grade gliomas (HGGs) treated with radiation and adjuvant chemotherapy remains poor. The expression of epidermal growth factor receptor (EGFR) has been established in children with HGGs. This report demonstrated the outcomes of adjuvant nimotuzumab, an EGFR inhibitor, with irinotecan in pediatric HGGs.
Methods Children with newly diagnosed HGGs were enrolled. Two weeks after surgery, nimotuzumab with a dose of 150 mg/m^2 was given every week during radiation. After completion of radiation, a 4-week cycle of nimotuzumab (150 mg/m^2) at week 1 and 3 and irinotecan (125 mg/m^2) at week 1, 2, and 3 was given.
Results Sixteen patients (5 females, 11 males), with a mean ± SD age of 8.2 ± 3.5 years were included. Tumors were located at the supratentorial region (50.0%), infratentorial region (43.8%), and both locations (6.2%). The 5-year PFS and OS were 19.9 ± 11.6 and 31.5 ± 13.0%, respectively. Median times of PFS and OS were 1.8 and 1.9 years, respectively. Prognostic factors related to good outcome were the location of tumor at the supratentorial region or outside brainstem and the extension of surgery. Side effects were minimal, with grade 1 anemia in three patients and diarrhea in one patient. Although, the adjuvant regimen of nimotuzumab and irinotecan slightly increases the overall outcome when compared to the historical study, the advantages of this protocol were minimal side effect, short period of hospitalization, and improved OS in patients who received extensive surgery.

Keywords High-grade gliomas · Chemotherapy · Outcome · Nimotuzumab

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Introduction

The outcome of patients with high-grade gliomas (HGGs) demonstrated a 5-year progression-free survival (PFS) of only 6 to 18% [1]. A randomized study of procarbazine, lomustine, and vincristine, or eight drugs in a 1-day protocol consisting of vincristine, carmustine, procarbazine, cytarabine, hydroxyurea, cisplatinum, dacarbazine, and methylprednisolone showed a 5-year overall survival (OS) of around 20% in HGGs, after central review [2]. Although the survival time remains poor, adjuvant chemotherapy has shown increased OS when compared to radiation alone [3]. The prognosis of HGGs is also dependent on the extension of surgery and location [1, 4, 5].

Irinotecan has been used as a single agent or in combination with other agents in the treatment of recurrent or newly diagnosed HGGs, with response rates varying from 7 to 21% [6–10]. Nimotuzumab, a humanized monoclonal antibody, binds to the epidermal growth factor receptor (EGFR), then inhibits activation of the protein tyrosine kinase. Nimotuzumab was initiated in children with resistant HGGs

at a dose of 150 mg/m^2/dose every week for 6 weeks, followed by a 3-week interval for four doses. The median survival time of responders was 10 months compared to 3.2 months for the non-responders [11]. Nimotuzumab is well tolerated, with reports of side effects such as mild or moderate skin rash, grade 1 and 2 mucositis, vomiting, seizure, and hypo or hyperthermia [12]. The study of nimotuzumab in combination with irinotecan in newly diagnosed HGGs in children is limited. The aim of this report was to demonstrate the OS of newly diagnosed with HGGs children treated with combination of nimotuzumab and irinotecan.

Materials and methods

Patients

Patients ≤18 years of age with newly diagnosed HGGs with histological confirmation gave informed consent and were enrolled. Patients were treated at the Faculty of Medicine Ramathobodi Hospital. EGFR status was determined by the immunohistochemistry method. This study was conducted between May 1, 2010 and January 1, 2016, and approved by the Institutional Review Board.

Treatment protocol

Two weeks after surgery, patients received the three-dimensional conformal radiotherapy at a dose of 55.8 to 59.4 Gy. Nimotuzumab at a dose of 150 mg/m^2 was administered every week during radiation. After radiation, a 4-week cycle of nimotuzumab (150 mg/m^2) at week 1 and 3 and irinotecan (125 mg/m^2) at week 1, 2, and 3 was given. The treatment was continued until the tumor progression or maximum of 1 year. The magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) studies were evaluated 4–6 weeks after completing radiation and at 3-month intervals or as indicated by clinical neurological examination. The toxicities from chemotherapy were monitored and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 [13].

Results

Sixteen patients (5 females, 11 males), mean ± SD for age of 8.2 ± 3.5 years, were enrolled. The most common diagnosis was glioblastoma multiforme (GBM). Tumors were located at the supratentorial region in 8 (50.0%) patients, the infratentorial region in 7 (43.8%) patients, and at both locations in 1 (6.3%) patient. Total tumor removal was performed in 3 patients, subtotal tumor removal in 2 patients, partial tumor removal in 3 patients, and biopsy alone in 8 patients. EGFR was positive in 9 (56.3%) patients (Table 1).

The median follow-up time was 1 (0.2–5.5) years. The median times of PFS and OS were 1.8 and 1.9 years, respectively. The overall 1-year, 2-year, and 5-year PFS were 52.4 ± 13.2, 37.4 ± 13.0, and 19.9 ± 11.6%, respectively. The overall 1-year, 2-year, and 5-year OS were 70.8 ± 12.4, 47.2 ± 13.9, and 31.5 ± 13.0%, respectively (Fig. 1).

The subgroup analysis, including age, gender, EGFR status, locations, and extension of surgery, was performed to determine the factors associated with increase survival. Patients who received total and near total tumor removal had significantly higher 5-year PFS (44.4 ± 22.2 vs 0%, $p = 0.006$) and OS rates (66.7 ± 19.2 vs 0%, $p = 0.015$) when compared to patients who received partial tumor removal or biopsy. Patients with tumors located at the supratentorial region had significantly higher 5-year OS rate of 66.7 ± 19.2%, $p = 0.026$ when compared with those with tumors located at infratentorial region (Fig. 2a). A similar finding was demonstrated on the tumor at brainstem when compared to the tumors located at other locations (Fig. 2b). No serious side effects were identified, with only grade 1 anemia found in 3 patients, and 1 patient developing irinotecan associated watery diarrhea which responded to 2–3 doses of loperamide.

Discussion

The present report demonstrated the outcomes of combination of nimotuzumab and irinotecan in newly diagnosed HGGs. Most of the patients were in the high risk of poor outcome as 62.5% had the histology of GBM and 50% underwent only biopsy. The 5-year PFS and OS rates in this report were 19.9 and 31.5%, respectively, with a median survival of 22.8 months. The median survival time in the present report was higher than the previous study using nimotuzumab during radiation (11.8 months for GBM and 16.5 months for AA) [14] and the other report of post radiation (17.8 months) [15]. Besides, the OS in the present report was slightly higher than the previous reported of adjuvant multi-agent chemotherapy protocols (5-year OS 20%). Therefore, the adjuvant nimotuzumab and irinotecan may add benefit in increasing survival of HGGs.

The extension of surgery, location, and histology are the prognostic factors in HGGs [1, 3–5]. In the present report, the extension of surgery as a total tumor removal or near total tumor removal, a prognostic factor associated with a good outcome, had a high OS rate of 66.7%. From the previous report, gross tumor removal in children with HGGs had the OS of 63% [16]. Tumors located at the supratentorial region or outside the brainstem in the present study also associated with a better OS when compared to infratentorial region or other locations, at 66.7%, because almost all infratentorial tumors (7 out of 8) were located at the brainstem which was difficult to

Table 1 Characteristics of 16 patients with high grade gliomas

Number	Time to presentation (month)	Presentation	Gender	EGFR	Diagnosis	Location	Age (year)	Surgery	FU time (year)	Outcome
1	1	Diplopia	M	Neg	GBM	Parietal	13.0	NTR	3.8	CR
2	1	ICP	M	Pos	GBM	Brainstem	4.1	Biopsy	0.4	Dead
3	12	Spastic tone	M	Pos	Anaplastic oligoastrocytoma	Frontal	5.0	GTR	4.9	CR
4	9	Diplopia	M	Neg	GBM	Lateral ventricle	8.0	NTR	5.5	CR
5	1	ICP	M	Pos	GBM	Brainstem	9.4	Biopsy	1.1	Dead
6	No data	Weakness	F	Pos	AA	Frontal	11.2	GTR	1.0	Dead
7	10	ICP	M	Pos	AA	Brainstem	4.7	NTR	1.8	Dead
8	0.2	Ptosis	M	Neg	AA	Brainstem	5.9	Biopsy	2.9	Dead
9	2	Weakness	M	Pos	GBM	Frontoparietal	7.9	GTR	3.0	PR
10	5	ICP	F	ND	GBM	Brainstem	9.8	Biopsy	1.0	Dead
11	0.5	Weakness	F	Neg	AA	Brainstem	3.8	Biopsy	2.0	Dead
12	2	ICP, seizure	M	ND	AA	Frontoparietal	14.2	Biopsy	0.9	Dead
13	1	ICP, seizure	M	Pos	GBM	Brainstem	5.5	Biopsy	0.2	Dead
14	1	ICP, seizure	F	Pos	GBM	Right frontal	6.0	Partial	0.3	PD
15	1	Weakness	F	Pos	GBM	Spine and suprasellar	13.8	Biopsy	0.3	PR
16	0.7	Diplopia	M	Neg	GBM	Parietal	9.5	Partial	0.8	PR

CR complete response, *EGFR* epidermal growth factor receptor, *F* female, FU time follow-up time, *GBM* glioblastoma multiforme, *GTR* gross total tumor removal, *ICP* increased intracranial pressure, *M* male, ND not done, *Neg* negative, *NTR* near total tumor removal, *PD* progressive disease, *Pos* positive, *PR* partial response

remove surgically. All patients whose tumors were located at the brainstem died from the tumor progression. The EGFR status in the present study did not associate with the outcome, similar to a previous report [16]. Therefore, the extension of surgery is essential for the outcome of HGGs.

The main side effects in a previous report of adjuvant chemotherapy was bone marrow suppression and neurotoxicity [17]. The side effect associated with long term treatment (up to 2 years) with nimotuzumab are skin rash and mucositis, reported in 5.7 and 4.5% of patients, respectively [12]. In the present study, side effects were minimal which may be due to shorter duration or the different population, with grade 1 hematologic toxicity and diarrhea from irinotecan in 1 patient.

Conclusion

Concurrent nimotuzumab and radiation treatment followed by nimotuzumab and irinotecan improved OS, although the 5-year OS was 31.5%, when compared to the previous treatment

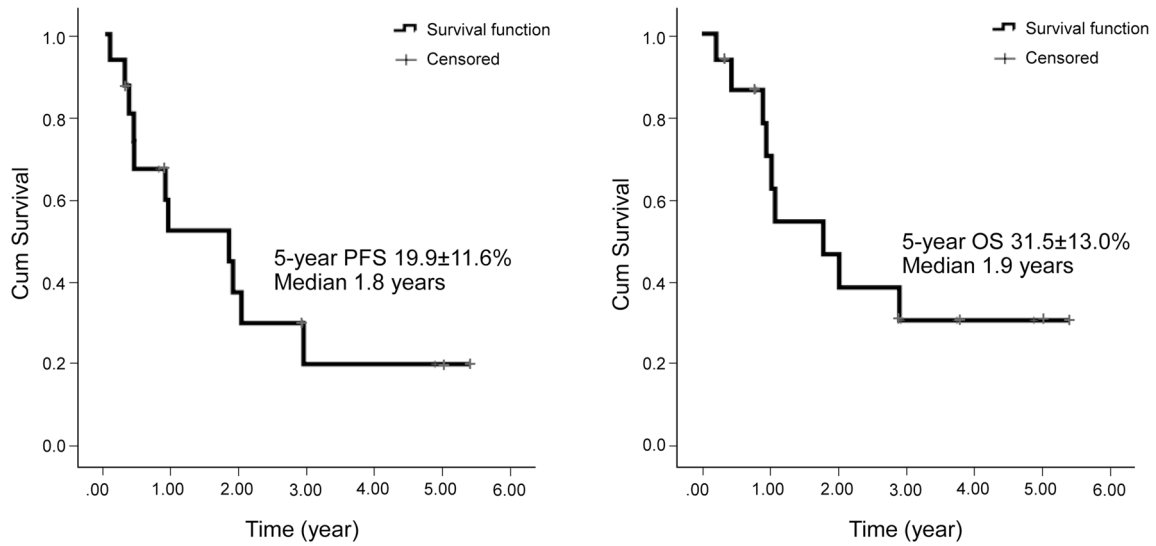

Fig. 1 The progression-free survival and overall survival of 16 patients

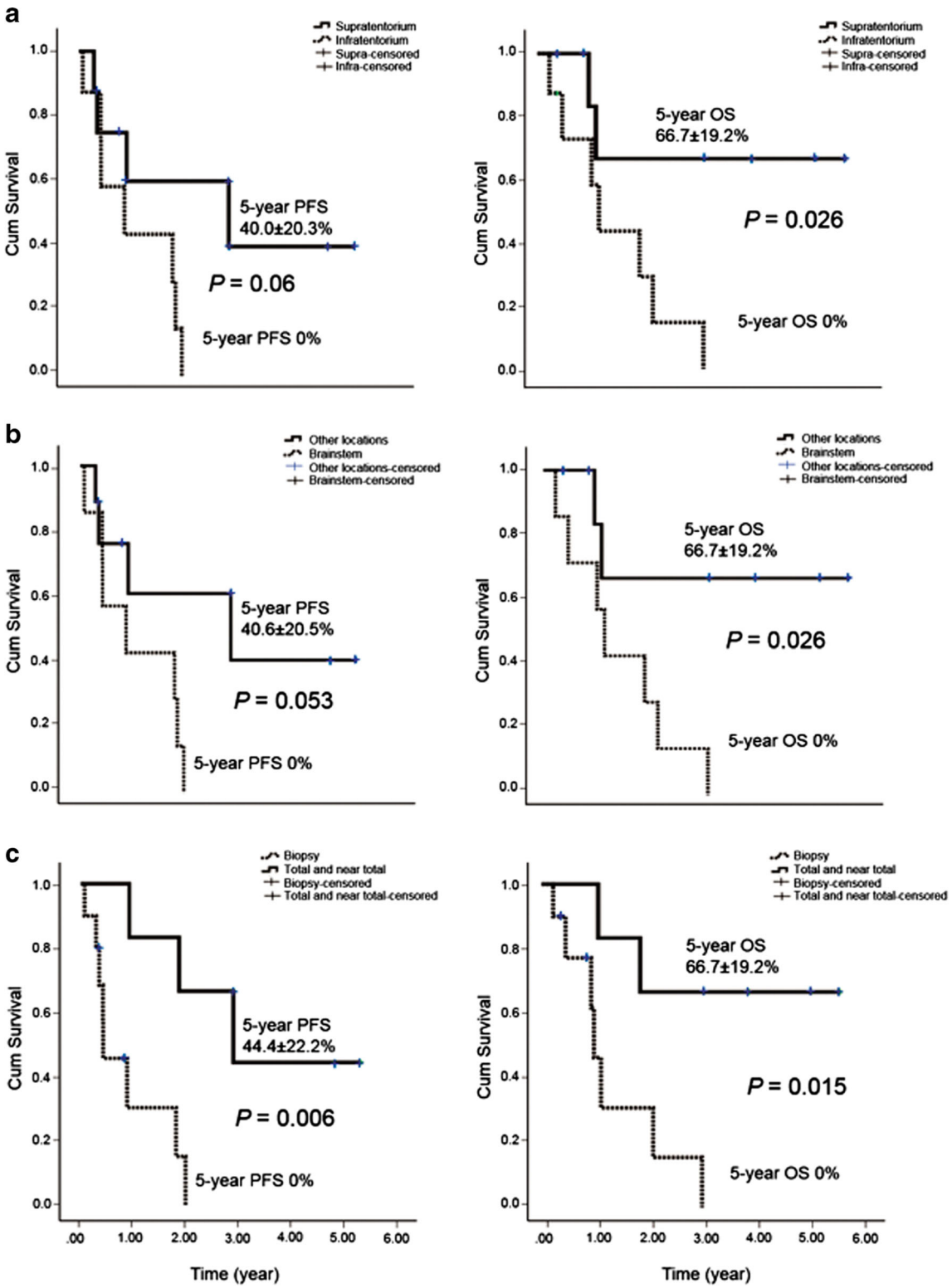

Fig. 2 The progression-free survival and overall survival of patients by *tumor location* (**a** supratentorium vs infratentorium) and (**b** brainstem vs other locations) and *extention of surgery* (**c**)

with minimal side effect and short period of admission. Patients who received total or near total tumor removal or whose tumors were located in the supratentorial area or tumors located outside the brainstem had longer OS which may be a selected group for adjuvant treatment in a limited resource country.

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Compliance with ethical standards This study was conducted between May 1, 2010 and January 1, 2016, and approved by the Institutional Review Board.

Conflict of interest The authors indicated no potential conflicts of interest.

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