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A Feasibility and Efficacy Study of Rapamycin and Erlotinib for Recurrent Pediatric Low-Grade Glioma (LGG)

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Background. To determine the toxicity and efficacy of rapamycin and erlotinib for the treatment of recurrent pediatric low-grade gliomas (LGGs). ***Methods.*** Patients <21 years of age with recurrent LGGs who had failed conventional treatment were eligible, including those with NF1. The treatment consisted of two phases, a feasibility portion which assessed the toxicity of erlotinib at 65 mg/m^2/day once daily and rapamycin at 0.8 mg/m^2/dose twice daily for 28 consecutive days. ***Results.*** Nineteen (19) patients, median age of 8 years, with recurrent LGGs received the two-drug regimen. Eight (8) of the patients had NF1. The combination of erlotinib and rapamycin was well tolerated and no patient was removed from study due to toxicity. All 19 patients were evaluable for response and one child, with NF1, had a partial response to treatment. Six (6) patients received the planned 12 courses of treatment. The reasons for stoppage of therapy before 1 year of treatment were poor compliance (1), parental desire for withdrawal (1), persistent vomiting which pre-dated initiation of therapy (1), and radiographic progression (10). In those patients with stabilization of disease for 12 months or greater, 3 stayed on therapy and ultimately developed progressive disease, and one patient stopped therapy at 12 months and progressed. Two (2) patients, both with NF1, have had >1 year disease control. ***Conclusions.*** The combination of rapamycin and erlotinib is well tolerated in children with LGGs. Objective responses were infrequent, although there was prolonged disease stabilization in some patients with LGGs, especially in two children with NF1. Pediatr Blood Cancer 2013;60:71–76.

Key words: erlotinib; low-grade gliomas; tarceva

INTRODUCTION

Low-grade gliomas (LGGs) are the most common childhood brain tumors, constituting 40% of all primary central nervous system tumors diagnosed in pediatric patients. The majority are pilocytic astrocytomas, but other histologic subtypes do occur. Arising in diverse brain locations, LGGs have a proclivity to originate in the diencephalon in infants and children <5 years of age. The treatment of choice for LGGs is gross total resection (GTR), with resultant progression-free survival and cure rates of 90–100% without adjuvant therapy [1]. However, radical resection is often not prudent when tumors are located in critical areas, including the brain stem, chiasm, and hypothalamus. The optimal therapy for these unresectable or residual progressive LGGs is less obvious [2]. For some patients with stable residual LGGs after surgery, observation alone is recommended, however, a prospective trial demonstrated that 5-year progression-free survival is only between 50% and 60% following partial resection [3].

Radiotherapy for children with subtotally resected or unresected LGGs has resulted in 5 and 10-year event-free survival (EFS) rates of 80–90% following conformal or stereotactic radiotherapy [4,5]. However, the use of radiotherapy in low-grade tumors, which are usually associated with long life expectancy, is problematic, particularly in young children due to concerns over the risks of long-term severe toxicities. Neurocognitive, endocrine, hearing, and cerebrovascular sequelae, as well as secondary malignancy [6,7], may occur after radiotherapy. Moreover, children with neurofibromatosis type 1 (NF1) who have a propensity to develop LGGs, predominantly of the visual pathway [8], have increased susceptibility to radiotherapy induced cerebrovascular complications and secondary tumors [9,10].

This has led to a shift away from radiotherapy towards chemotherapy with the aim of stabilizing disease and either avoiding or delaying radiotherapy. The most frequently used frontline chemotherapy involves a combination of carboplatin and vincristine, which is successful in delaying radiation therapy. The combination has resulted in a 3 year EFS of 60–70% [11] which falls to 35–61% at 5 years [12,13]; thus, within 5 years, one-half or more of children require further therapy for tumor control. Furthermore, patients may develop carboplatin-related allergies and require alternative treatments early in the course of treatment [11–13].

Other chemotherapy regimens that have shown efficacy in newly diagnosed and recurrent patients include vinblastine [14], TPCV (Thioguanine, Procarbazine, Lomustine, and Vincristine) [15], the combination of cisplatin and etoposide [16,17], and temozolomide [18]. However, these approaches are associated with risks. Cisplatin-induced hearing loss is of particular concern in patients with pre-existing visual impairment. Recently, the combination of bevacizumab (Avastin) and irinotecan displayed promising objective responses; however, the long-term benefits and side-effects of this combination are still unknown [19].

Alternative therapies that selectively target the molecular underpinnings of the tumor's biology are needed. Tissue

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microarrays from paraffin-embedded tumor specimens obtained from 63 newly diagnosed LGG patients showed high expression of epidermal growth factor receptor (EGFR) and phosphorylated-EGFR in 87.1% and 30.6% of LGGs, respectively as well as a high expression of mTOR in 77.4% of LGG tumors [20]. In NF1, the importance of mTOR may be even more prominent, since neurofibromin regulates mTOR via Ras signaling, and mTOR pathway activation is observed in primary mouse Nf1-deficient astrocytes. The combination of EGFR and mTOR inhibition has been shown to be synergistic in its inhibition of mTOR induced AKT activation [21]. Thus, there is pre-clinical rationale for combining therapies targeted at mTOR and EGFR.

Erlotinib is an EGFR inhibitor that has been evaluated in pediatric-aged patients by the Children's Oncology Group. In a Phase 1 study, the MTD was found to be 85 mg/m^2 as a single agent and 65 mg/m^2 was well tolerated in that study. Rapamycin is an mTOR inhibitor that has been extensively used in children after organ transplantation to prevent graft rejection. Both drugs are available orally and are usually well tolerated. This study evaluated the toxicity and potential efficacy of combining erlotinib and rapamycin in children with progressive LGGs for whom initial treatment had failed.

PATIENTS AND METHODS

Eligibility Criteria

To be eligible, patients had to be younger than 21 years, with recurrent LGGs. Both patients with and without NF1 were eligible. Patients without NF1 were required to have histological confirmation of a low-grade glial tumor, with the exception of optic pathway tumors. Patients with NF1 with MRI demonstrated lesions that were consistent with a low-grade glial tumor, could be entered on study without histological verification.

All patients had to have failed at least one regimen of conventional therapy, including radiotherapy or chemotherapy, to be eligible. Patients required satisfactory organ function including bone marrow function (absolute neutrophil count (ANC) $>$1,000/μl, platelet count $>$100,000/μl, and hemoglobin $>$8 g/dl), liver function (GPT $<$2.5 and bilirubin $<$1.5, the upper limit of normal), renal function (normal serum creatinine for age) and an adequate performance status (Karnofsky or Lansky score of $\geq$50%). Key exclusion criteria included another active tumor or uncontrolled infection. The study had IRB approval at all sites and all patients, and/or their parents or legal guardian, signed an informed consent form.

Treatment Plan

The treatment plan consisted of two phases; a feasibility portion, which was essentially a safety window study, and a Phase 2 portion.

Feasibility component. In the feasibility portion of the study, the tolerability of the combination of erlotinib and rapamycin was evaluated in a cohort of three patients. Erlotinib was given at 65 mg/m^2/day, once daily for 28 consecutive days. Erlotinib could only be taken with water, over the concern that food could impact its bioavailability. If no dose-limiting toxicities were noted after the first 28 days of treatment of erlotinib alone, rapamycin was added at initial dose of 0.8 mg/m^2/dose twice daily, and dosage was pharmacologically adjusted on a weekly basis to maintain a trough rapamycin level between 10 and 15 ng/ml. Once the level was found to be within the target range on two consecutive assessments, monthly rapamycin levels were to be obtained. The staggered starting schema was used to try to separate the toxicity of erlotinib alone from that of the combination of the two agents.

Patients remained on the combination of erlotinib and rapamycin for 28 consecutive days, and at the completion of 28 days of combination therapy, assessment for feasibility of moving to the Phase 2 component of the study was completed. If no dose-limiting toxicities were seen after 2 months of treatment, including 1 month of combination erlotinib and rapamycin treatment, then the feasibility portion of the study was to close and the Phase 2 study was to commence. If one dose-limiting event was encountered, in the first three patients, which did not resolve within 7 days, then a second cohort of three patients were to be treated in the feasibility portion of the study. If two or more patients developed dose-limiting toxicity at 65 mg/m^2, then another cohort of patients was to open at an erlotinib dose of 50 mg/m^2. The rapamycin dose was not to be lowered. If undue toxicity was seen with the combination of erlotinib at 50 mg/m^2 and rapamycin, the study was to be closed.

Phase 2 component. The Phase 2 component consisted of treatment with erlotinib at 65 mg/m^2/day over 28 consecutive days, rapamycin was added during the second month of treatment. The combination was to be continued for 12 months, as long as there was no significant toxicity or evidence of progressive disease. The study was designed to enter a maximum of 24 evaluable patients. There was no planned interim analysis but there was yearly evaluation by an independent Data Safety Monitoring Board (DSMB).

Those patients who tolerated the erlotinib and rapamycin during the first 2 months of treatment (including the 1 month of combined treatment) would remain on treatment without breaks for 12 months, as long as there was no significant toxicity and no evidence of progressive disease.

Patient Assessments: Evaluation of Toxicity and Response

Safety assessments included physical and laboratory evaluations. Vital signs, physical examinations, and laboratory evaluation consisting of complete blood counts and serum electrolytes were performed prior to every course (28 days). Liver functions and renal functions were performed prior to initiation of therapy, every 2 weeks for the first two courses and then before each course (every 4 weeks). Urinalysis, fasting cholesterol, and lipoprotein profiles were drawn prior to initiation of therapy and then before courses 3, 6, 9, and 12. Adverse events were evaluated according to the NCI common toxicity criteria (CTCAE v3.0).

Response assessments included clinical and radiological evaluations. Neurological examinations were performed prior to every course. In patients with visual pathway tumors, neuro-ophthalmological assessments were performed every three courses. An evaluation of the change in the greatest bi-directional area of the tumor as seen on MRI was performed after 1 month of treatment with erlotinib alone (to be sure there was no loss of disease control after initial treatment) after 2 months of treatment (1 month of combination therapy) and every 2 months, thereafter. The contrast enhancing portion of the tumor or the extent of tumor defined on noncontrast FLAIR/T2 images (whichever was

greater) was measured and responses were classified as follows: CR (complete response): complete disappearance of tumor; PR (partial response): ≥50% reduction in the bi-directional measurement of the tumor (area); MR (minor response): ≥25%, but <50% reduction in tumor size; SD (stable disease): from 0% to <25% reduction in tumor size, or 0% to <25% increase in tumor size; PD (progressive disease): ≥25% increase in tumor size.

Patients were also considered to have progressive disease if there was neurological or visual deterioration believed to be secondary to tumor growth, even without radiographic progression. Visual deterioration was defined as either a drop in visual acuity of greater than two lines on a visual acuity chart or a demonstrable loss in the visual field.

RESULTS

Patient Characteristics

Twenty-one (21) patients with recurrent low-grade glioma were recruited, between September 2007 and July 2010, from three institutions: Children's National Medical Center, Washington DC, United States; Children's Hospital at Westmead, Sydney, Australia; and Sheba Medical Center, Tel-Hashomer, Israel. Two (2) of the 21 patients withdrew consent prior to initiation of therapy.

The relevant demographic and clinical characteristics of the patients included in the study are listed in Table I. Patients' ages were between 3 and 16 years. Eight (8) of the patients had NF1. Histology in the 11 nonNF1 patients was juvenile pilocytic astrocytoma (9) and fibrillary astrocytoma (2). Tumors were located as noted in Table I.

All 19 patients had initially been treated with the vincristine–carboplatin combination as first line chemotherapy. Eight patients had also received at least one other form of chemotherapy prior to their inclusion in the present study and one patient had received radiotherapy. All patients had been off any cytotoxic medications for at least 4 weeks prior to the initiation of erlotinib.

Toxicity

All 19 patients who received the study regimen were included in the report of toxicities (Table II). The combination of erlotinib and rapamycin was generally well tolerated. None of the patients were removed from the study due to toxicity and no one manifested Grade 4 adverse events (AEs).

During the feasibility component of the study, the three patients entered on study had no dose-limiting toxicity at the prescribed dose of erlotinib and rapamycin during the first 2 months of treatment, and the Phase II component was opened. Two patients developed Grade 3 AEs, which were possibly related to the study regimen, both during maintenance therapy. One patient, who was not neutropenic or lymphopenic at the time, manifested Grade 3 cellulitis, which was treated by antibiotics and interruption of erlotinib and rapamycin for 1 month, and the second patient developed transient neutropenia from which he recovered within 7 days. Sixteen out of 19 patients suffered from at least one Grade 1 or 2 toxicity. Of the Grade 1–2 AEs, the most common were rash which occurred in 11 patients (frequently acneiform), oral aphthous ulcers that developed in nine patients and gastrointestinal tract manifestations, predominantly diarrhea, which was encountered in seven patients. Other less common Grade 1–2 AE toxicities are as noted in the table.

TABLE I. Patients' Demographics (N = 19)

	NF1 (N = 8)	Not NF1 (N = 11)
Median age (range) yrs	6.1 (3–14.9)	8.5 (3–16)
Location		
Chiasm	3	4
Thalamus	0	3
Brain stem	4	2
Diencephalic	1	0
Disseminated	0	2
Number or prior chemotherapies		
1	5	6
2	3	3
3	0	2
Radiotherapy	0	1

TABLE II. Adverse Events

	n (%), n = 19
Grade 3 adverse events	
Cellulitis	1 (5)
Neutropenia	1 (5)
Grade 1 and 2 adverse events	
Rash	11 (58)
Oral aphthous ulcers	9 (47)
GIT symptoms[a]	7 (37)
Paronichia	2 (10)
Neutropenia	1 (5)
Hypertriglyceridemia	1 (5)
Hypercholesterolemia	1 (5)

[a]GIT, gastrointestinal tract.

Response/Time to Progression

Since the initial three patients on the feasibility component of the study were treated at the dose given to patients on the Phase II component, their response data was combined with the 16 patients treated on the Phase II study; thus, a total of 19 patients were evaluable for response assessment.

Six (6) patients received the 12 planned courses (1 year of treatment), while 13 patients stopped the treatment earlier due to either progressive disease (10) or due to parental withdrawal of consent (1), poor compliance (1), or persistent vomiting (which predated initiation of study in one child with a cervicomedullary tumor who had stable disease while on study). Radiographic response was observed in one patient with a PR who had NF1, after wo cycles of treatment (see Fig. 1); only one child progressed at the first neuroradiographic evaluation of combined therapy (2 months after initiation of treatment).

In 10 evaluable patients who progressed on treatment, disease progression was seen a median of 6 months from initiation of treatment (range 3–9 months). Of the six who completed the year of treatment three had NF1. Four of the six patients ultimately developed progressive disease, either on therapy (13, 16, and

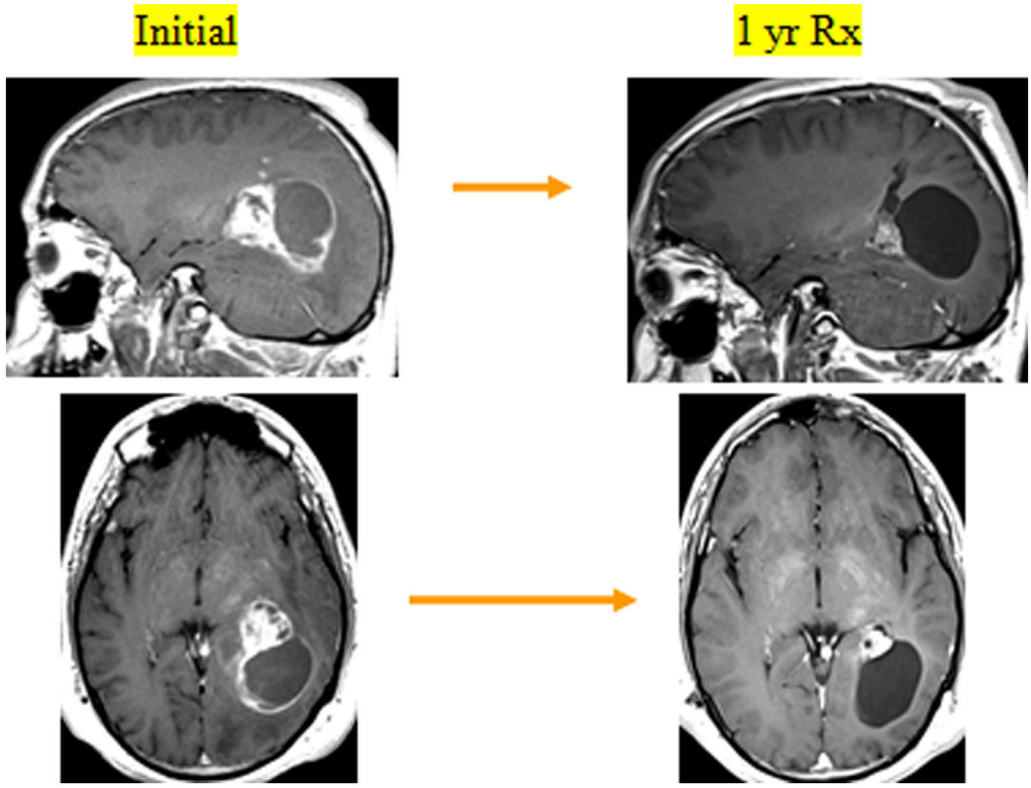

Fig. 1. Saggital and axial enhanced MRI's of a patient on study showing a partial response after 2 months of treatment.

18 months after beginning therapy) or after cessation of therapy (at 12 months). The child who had received radiotherapy 1 year earlier had 4 months of stable disease. Two patients, both with NF1, one with a brain stem glioma and another with a diencephalic glioma, remain progression free off treatment for greater than 1 year at time of submission of the manuscript—including the child with the PR. Specifically, a 14-year old male with NF1 had received carboplatin and vincristine for a visual pathway glioma at age 4 and was off all treatment for 9 years, when he developed an enhancing mass in the diencephalon associated with headaches, lethargy, and nausea. The mass was biopsied and found to be a pilocytic astrocytoma, with a mitotic index of 5–10%. He began treatment with the erlotinib/rapamycin regimen and had a partial response to treatment (Fig. 1). He was treated for 1 year and has been off treatment, without evidence of progression, for 30+ months. The second child with prolonged disease control was a 13-year-old female with NF1, who presented with right hemiparesis and a focal enhancing mass involving the left half of the midbrain. She was not biopsied, but treated with 10 weeks of carboplatin and vincristine. The mass enlarged by 20% and the hemiparesis worsened. Four weeks after stopping the carboplatin and vincristine, she began the tarceva/rapamycin. The tumor decreased by nearly 25% and her hemiparesis improved and ultimately disappeared. She stopped treatment after 12 months and maintains disease control for 22+ months off treatment. The study was closed after only one objective response was seen in the first 19 evaluable patients.

CONCLUSIONS

This study evaluated erlotinib, an EGFR tyrosine kinase inhibitor, in combination with rapamycin, an mTOR inhibitor, for recurrent LGG patients. The hypothesis underlying this combination regimen was that concurrently targeting upstream and downstream mediators is more likely to suppress PI3K-AKT signaling and thus would be more effective in controlling the proliferation of LGGs than either agent alone. The study demonstrated that the combination of erlotinib and rapamycin was in general well tolerated in the pediatric population. None of the patients was removed from the study due to toxicity and no child suffered a Grade 4 adverse event. Grade 1 or 2 adverse events either resolved spontaneously or became less bothersome despite continuation of the therapy. Only two patients suffered Grade 3 adverse events and they resolved upon discontinuation of the treatment and did not recur upon retreatment.

The efficacy of the combined therapy was equivocal. Radiographic objective response occurred only in one child, six patients had stable disease for 1 year on therapy, two of whom maintained disease control for months after completion of treatment; both are still free of progressive disease greater than 12 months after cessation of therapy. Both patients who had prolonged benefit had NF1. The significance of stable disease in children with LGGs, especially those with NF1, is difficult to assess. Some patients with LGG and NF1 will have periods of stability after radiographic progression and even spontaneous involution has

been noted. However, both NF1 patients had radiographically proven progression prior to study entry, had lesions in regions of the brain where spontaneous regression has not been frequently reported (brain stem and thalamus), and were older (14.5 and 15 years of age).

Results of preclinical in-vitro studies demonstrate that the combination of rapamycin and EGFR inhibitors provide enhanced anti-tumor efficacy in several cell lines, including renal cell carcinoma, lung cancer, and glioblastoma multiforme [22,23]. Despite the encouraging preclinical data supporting the rationale of combining an EGFR inhibitor with an mTOR inhibitor, clinical results in other settings have been disappointing. For instance, a Phase 2 trial of erlotinib plus rapamycin in adults with recurrent glioblastoma demonstrated that the combination was well tolerated in 32 patients but showed negligible activity; no patients achieved either a CR or PR and the 6-month progression-free survival was 3.1% [24]. Another Phase 2 trial assessed the efficacy of the combination of another EGFR inhibitor, gefitinib, and a different mTOR inhibitor, everolimus, in patients with advanced nonsmall cell lung cancer. The 13% partial response rate observed in these patients did not meet the predetermined response threshold to pursue further study [25].

Several factors may underlie the somewhat disappointing outcome of the current study. The blood brain barrier may limit central nervous system (CNS) penetration of erlotinib. Cerebrospinal fluid (CSF) penetration of erlotinib and its active metabolite OSI-420 were 6.9% and 8.6%, respectively, in a child with high-grade glioma who received 75 mg/m^2/day of erlotinib [26]. Although preclinical studies have reported inhibitory effects of erlotinib against several cancer cell lines at concentrations similar to those reached in the CSF of this patient [27], these CSF concentrations achieved may be insufficient for therapeutic effect in vivo. Indeed, several reports conclude that intermittent, high-dose erlotinib improved CNS metastases that were resistant to continuous, normal-dose erlotinib [28,29]. It can be argued that the dose of erlotinib used was too low, as 85 mg/m^2 was found to be the MTD by a COG study using the drug in isolation [30]. Reviewing the toxicity profiles of that study, it was decided to drop back one level for this combination trial. There are no dose response relationships known for erlotinib. Similarly, the optimal dose of rapamycin for disease control in children with any form of brain tumor is unknown, and the dose found safe in patients utilizing the drug for other indications was adopted.

Other reasons for the results of the study may include the heterogeneity of target expression within and across tumors, complexity of signaling cascades including redundancy and cross-talk, and resistance mediated by compensatory up-regulation of alternative pathway mediators. The mTOR complex, which regulates cell growth and proliferation, exists in two distinct complexes within the cells: mTORC1, which is sensitive to rapamycin and mTORC2, which is resistant to rapamycin. Blockade of mTORC1 interactions with raptor by rapamycin could shift the equilibrium toward the mTORC2–rictor-bound complex, which encourages cell survival by increasing Akt phosphorylation. Therefore, rapamycin can be thought of as possessing two counteractive activities toward tumor cell growth, one that inhibits cell proliferation and one that activates prosurvival signals [31]. Dual effective inhibition of mTOR and AKT or mTORC1 and mTORC2 may be required for tumor control. It was also recently shown that NF1 loss leads to neural stem cell (NSC) proliferation and gliogenesis in the brainstem, but not the cortex, through differential upregulation of specific genes (rictor) and preferential mTOR-mediated activation of Akt in brainstem NSCs [32,33].

In conclusion, the combination of erlotinib and rapamycin, given at the dosing and sequencing as outlined in this study was quite tolerable, but had questionable to no activity in children with progressive sporadic LGGs, with some experiencing a few months of stable disease. In children with NF1, one child had a clear-cut objective response and two of eight experienced prolonged disease control off therapy.

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