Pediatric Phase II Trials of Poly-ICLC in the Management of Newly Diagnosed and Recurrent Brain Tumors

Lisa L. R. Hartman, University of California San Diego
John R. Crawford, University of California San Diego
Milan T. Makale, University of California San Diego
Mehrzad Milburn, University of California San Diego
Shweta Joshi, University of California San Diego
Andres M. Salazar, Childrens Hospital of Orange County
Beth Hasenauer, Childrens Hospital of Orange County
Scott R. VandenBerg, University of California San Diego
Tobey MacDonald, Emory University
Donald L. Durden, University of California San Diego

Journal Title: Journal of Pediatric Hematology/Oncology
Volume: Volume 36, Number 6
Publisher: Lippincott, Williams & Wilkins | 2014-08-01, Pages 451-457
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1097/MPH.0000000000000047
Permanent URL: https://pid.emory.edu/ark:/25593/tvhj9

Final published version: http://dx.doi.org/10.1097/MPH.0000000000000047

Copyright information:
Copyright © 2014 by Lippincott Williams & Wilkins.

Accessed October 12, 2019 3:12 AM EDT
Pediatric Phase II Trials of Poly-ICLC in the Management of Newly Diagnosed and Recurrent Brain Tumors

Lisa L.R. Hartman, MD†, John R. Crawford, MD‡, Milan T. Makale, PhD§, Mehrzad Milburn, BSN, CCRC†, Shweta Joshi, PhD†, Andres M. Salazar, MD||, Beth Hasenauer, MS†, Scott R. VandenBerg, MD, PhD‡, Tobey J. MacDonald, MD∗∗, and Donald L. Durden, MD, PhD∗,†

†Department of Pediatrics, Rady Children’s Hospital, University of California San Diego, La Jolla, CA

‡Department of Neuro-oncology, Rady Children’s Hospital, University of California San Diego, La Jolla, CA

§Department of Neuro-oncology, Rady Children’s Hospital, University of California San Diego, La Jolla, CA

||Oncovir Inc.

∗Children’s Oncology Group, Childrens Hospital of Orange County, Orange, CA

**Department of Pediatrics, Emory University, AFLAC Cancer Center, Children’s Healthcare of Atlanta, Atlanta, GA

Summary

Brain tumors are the most common solid tumor diagnosed in childhood that account for significant morbidity and mortality. New therapies are urgently needed; hence, we conducted the first ever prospective open-label phase II trials of the biological response modifier, poly-ICLC, in children with brain tumors. Poly-ICLC is a synthetic double-stranded RNA that has direct antiviral, antineoplastic, and immune adjuvant effects. A total of 47 children representing a variety of brain tumor histopathologic subtypes were treated with poly-ICLC. On the basis of the results of the initial phase II trial, an expanded prospective phase II trial in low-grade glioma (LGG) has been initiated. MRI was used to acquire volume-based measures of tumor response. No dose-limiting toxicities have been observed. In the initial study 3 of 12 subjects with progressive high-grade
gliomas (HGGs) responded, and 2 of 4 children with progressive LGG experienced stable disease for 18 to 24 months. In the follow-up LGG phase II study, 2 of 5 LGG patients were stable over 18 months, with 1 stable for 6 months. Overall 5 of 10 LGG patients have responded. On the basis of low toxicity and the promising LGG response, poly-ICLC may be effective for childhood LGG, and the results justify biomarker studies for personalization of poly-ICLC as a single agent or adjuvant.

**Keywords**

poly-ICLC; toll receptor; pediatric gliomas; phase I/II; toxicity

Brain tumors are the most common pediatric solid tumor and account for significant childhood morbidity and mortality in the United States. The 2007 WHO classification grades central nervous system tumors from I to IV based on proliferative potential, infiltrative nature, nuclear atypia, and mitotic activity.1 Gliomas as a broad category account for 53% and 38% of brain tumors seen in children and adolescents, respectively.2 Some lower grade tumors, such as grade II diffuse astrocytomas, have the potential to transform into higher grade (IV) tumors such as anaplastic astrocytoma and glioblastoma.1 Treatment generally consists of surgery followed by either chemotherapy and/or radiotherapy and is associated with severe morbidity and risk of late effects. Newer forms of treatment are desperately needed, and we report results from the first prospective pediatric phase II trials of the biological response modifier poly-ICLC for newly diagnosed and recurrent brain tumors and low-grade glioma (LGG) cohorts.

Poly-ICLC is a synthetic complex of polyinosinic-polycytidylic acid stabilized with poly-lysine and carboxymethyl cellulose. This double-stranded RNA molecule directly suppresses tumor cell proliferation, and this is hypothesized to partly derive from interferon induction, while the overall antitumor effect also stems from immune enhancement. Poly-ICLC may activate/amplify the antibody response to antigen, and thus potentiate the activation of natural killer cells, T cells, macrophages, and cytokines.3–5 Poly-ICLC was used as an interferon inducer at high doses (up to 300 mcg/kg, IV) in short-term cancer trials in the 1980s, but these trials gave mixed results with moderate toxicity, and the use of poly-ICLC was generally abandoned.6–8

We initially tested poly-ICLC for the first time in pediatric brain tumor patients nearly 2 decades ago and acquired promising data. At that time renewed interest in poly-ICLC was spurred by the demonstration that intramuscular (IM) administration significantly reduced treatment side effects, and that lower doses (10 to 50 mcg/kg) of poly-ICLC are able to regulate adaptive immune responses, stimulate host defenses, and directly enhance interferon-independent immunity.9,10 Despite a dramatic clinical response that we observed in 2 of 4 patients with LGG, at the conclusion of our initial study we were not convinced from the 2 of 4 responders in the LGG cohort alone that poly-ICLC had activity. However, we were recently motivated to revisit the use of poly-ICLC in brain tumors for 3 reasons: (1) a persistent lack of therapeutic agents other than carboplatinum/Vcr or vinblastine regimens that can only be given for a limited number of cycles due to bone marrow toxicity,11 (2)
poly-ICLC is now known to be a ligand for the toll-like receptor 3 (TLR3) and there has been a rapid expansion of data addressing the major biological role of TLR3, and advances in genetic profiling and microarray analysis now potentially facilitate the identification of biomarkers supporting the effective substratification of responsive patient response groups. Our rationale is that the initial adult and pediatric poly-ICLC results in brain tumors were promising, and now the feasibility of identifying response biomarkers and deciphering TLR3-related pathways may support the rational use of poly-ICLC both as a single agent and in combination therapy.

The efficacy of poly-ICLC has never been prospectively evaluated in children with brain tumors outside of the present study, although in some adult clinical trials it was active against a range of newly diagnosed and recurrent brain tumors. The safety and tolerability of long-term, low-dose intramuscularly administered poly-ICLC in the dose range of 20 mcg/kg 2 to 3 times weekly, in adult patients with malignant gliomas was established. Prolonged, quality survival with tumor stabilization or regression confirmed by magnetic resonance imaging for most patients with anaplastic astrocytomas and glioblastomas prompted Salazar et al to conclude that more extensive laboratory and controlled clinical studies with poly-ICLC are warranted. Other adult trials with recurrent and newly diagnosed glioblastoma found that poly-ICLC was well tolerated as a single agent and in combination, but did not improve progression-free survival. This warrants substratification of responsive patient groups and an examination of poly-ICLC in the pediatric population as there are often age-related differences in the biology of cancer and in pharmacokinetics, pharmacodynamics, and efficacy of therapeutics.

The 2 trials summarized in the present report are the only prospective phase II studies of poly-ICLC ever performed in a pediatric brain tumor population. The results align positively with the primary purposes of phase II testing that are to confirm safety and determine whether the agent under consideration exhibits a clinically relevant effect. In this context, the key findings were the low systemic toxicity of poly-ICLC and the induction of stable disease in 4 of 9 LGG patients for over 18 months, with an additional patient stable for 6 months. Thus, we anticipate that poly-ICLC may have a beneficial role in children with LGG while minimizing treatment side effects. These findings support expansion of the current LGG trial, and the implementation of biomarker studies to: (1) further delineate the most responsive target patient substrata, and (2) elucidate pathways relevant to poly-ICLC in the context of TLR3 signaling and treatment resistance.

**METHODS**

**Patient Eligibility**

Patients 21 years old or younger with either newly diagnosed glioblastoma multiforme, anaplastic astrocytoma, diffuse intrinsic pontine glioma (DIPG), or any recurrent primary brain tumors with active growth who have failed prior therapy were eligible for this trial. Histologic confirmation from original diagnosis was required except for patients with radiographic evidence of a DIPG. Measurable tumor and evidence of disease by clinical, radiographic, or histologic criteria were required for eligibility.
Patients were required to have a life expectancy of at least 8 weeks, have an ECOG performance status of ≤2, and have recovered from the toxic effects of all prior therapy. Patients were also required to have adequate bone marrow function at study entry, defined as ANC ≥1000/mm^3, platelets ≥75,000/μL (transfusion independent), and hemoglobin >8.0 gm/dL (may receive PRBC transfusions). Serum creatinine and total bilirubin ≤1.5× normal, and AST and ALT<2.5× normal were also required. Female patients of childbearing age were required to use effective birth control measures if sexually active. Patients receiving other experimental immunotherapy or concurrent chemotherapy or radiation were excluded from this study. Subjects were also excluded if they had fever at the time of study entry. This study was approved by the local Institutional Review Board and written informed consent was obtained from all patients and/or their parents or legal guardians in accordance with institutional guidelines.

**Study Design**

The initial study was a prospective open-label phase II single-institution trial to estimate the response rate of poly-ICLC in 5 brain tumor strata. A phase I dose escalation study was not performed in the pediatric population based on the fact that poly-ICLC is not a chemotherapy drug, hence the usual concept of maximum-tolerated dose does not apply. We sought an optimum biological dose. In multiple previous reports it was shown that poly-ICLC induced greater activation of natural killer cells at 10 mcg/kg as compared with higher doses, and the most active biological dose of 20 mcg/kg was established in adult trials.\(^{14,21}\) The FDA agreed with this plan to do a low-dose study without a phase I dose escalation.

Response outcomes were expected to vary, so patients were stratified into 5 disease cohorts: recurrent HGG (anaplastic astrocytoma and glioblastoma multiforme), recurrent LGG, newly diagnosed DIPG, recurrent primitive neuroectodermal tumor (PNET)/ependymoma, and patients with neurofibromatosis. A follow-up open-label phase II multiinstitution study is currently ongoing with an expanded cohort of patients with the most responsive disease category in the initial phase II trial, recurrent and refractory LGG.

Poly-ICLC was administered the same way in both studies that were approved by the institutional committee for the protection of human subjects. The drug is supplied by Oncovir in sterile 1mL vials of 2 mg/mL opalescent solution. Dosing is a single 20 mcg/kg IM injection twice per week for up to 2 years duration. Total treatment course is divided into 4-week cycles. Monitoring for treatment-related toxicity has included history and physical examination with neurological assessment every 2 weeks for the first month and then before each cycle. Laboratory tests including serum chemistries and complete blood counts entailed weekly monitoring for the first cycle, every 2 weeks for cycle 2, and then monthly thereafter if stable.

**Response Criteria**

Tumor burden was measured radiographically by MRI, with/without gadolinium at baseline (pretreatment) and at the end of cycles 3, 6, 9, 12, 16, 20, and 24 while each patient remained on study. Response (percent change in tumor size from baseline) was determined from bidimensional measurements on the follow-up scan with the best response compared...
with the tumor size in the pretreatment MRI scan. The response criteria including bidimensional measurements of MRI, neurological examination, and steroid usage are listed in Table 1. Time-to-progression was defined as the duration of time between the starting date of therapy and the date that clinical or radiographic disease progression was first documented.

**Toxicity Evaluation**

Clinical and laboratory adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3. Toxicity was fully evaluated throughout the study duration and included measures of neurological status and blood hematologic and biochemical panels including liver and kidney function. Subjects were routinely monitored so that unacceptable toxicity could be rapidly identified and the subject removed from the study if deemed necessary on clinical or toxicity grounds.

**Statistical Methods**

For the initial study Simon’s optimal 2-stage design was used to evaluate MRI-based measures of poly-ICLC, and was intended to rule out \( p_0 \), an uninteresting level of response, in favor of \( p_1 \), a targeted level of response, that is, detectable tumor shrinkage. The first stage of accrual was designed to include 15 patients. If a tumor response in terms of MRI volume was observed in 1 to 3 of the first 15 patients evaluable, accrual would include an additional 20 patients. Poly-ICLC would be considered ineffective if 0 of the first evaluable subjects or 4 or less of the entire cohort responded. If 5 or more total subjects responded, the trial would be terminated and would be interpreted as having generated results consistent with efficacy.

In the expanded LGG cohort study response rates are compared with those seen historically with a similar patient population. The first stage of accrual is designed to include 9 patients with recurrent LGG. A positive response is defined as stable disease for >6 months or a partial response (PR) or complete response (CR). If a positive response (CR or PR) is observed in at least 1 subject, the trial will continue to enroll an additional 15 patients.

**RESULTS**

**Patient Characteristics—Initial Study**

Between April 1996 and May 2000, patients with pediatric brain tumors of all histopathologic subtypes were recruited from the outpatient clinic at Children’s Hospital Los Angeles. We enrolled 47 patients, of which 32 were evaluable for disease response (68%). In the initial study design, patients were considered evaluable for response to poly-ICLC therapy if they completed 4 weeks of therapy, and were deemed evaluable for toxicity if they completed 2 weeks of therapy. In our most recent phase II study in LGG, patients receiving 12 weeks of study drug are evaluated for response and after 4 weeks of study drug for toxicity. Nonevaluable patients in the original phase II study were composed of 2 categories: (1) patients who had progressive disease before the 4-week time point (8 patients) and (2) patients in which protocol violation resulted in off study status as dictated by our IRB (7 patients). A breakdown of the 8 patients with progressive disease before 4
weeks of therapy includes: (1) 2 patients with HGG, progressive disease on days 10 and 23 of therapy, (2) 2 patients with DIPG, progressive disease on days 15 and 23 of therapy, (3) 2 patients with undifferentiated malignant brain tumor, progressive disease on days 15 and 22 of therapy, (4) 1 patient with germinoma, progressive disease on day 27 of therapy, and (5) 1 patient with posterior fossa PNET, progressive disease on day 22 of therapy. None of these patients were within the LGG cohort. Our IRB required patients to come off study if a protocol deviation occurred. Protocol deviations included 3 patients who did not get prestudy creatinine. Their diagnoses included, anaplastic astrocytoma (cohort 1), chordoma (cohort 4), and recurrent DIPG (cohort 3). The other 4 patients removed from study due to protocol deviation included 1 patient each with diagnosis of LGG, HGG and 2 patients with DIPG.

Of the 32 remaining patients evaluable for response, 12 had HGG, 4 had low-grade astrocytoma, 8 had DIPG, 2 had PNET, 3 had ependymoma, 1 had brainstem mass of undetermined pathology, 1 had anaplastic oligoastrocytoma, and 1 had neurofibromatosis-associated tumors. Eight patients had newly diagnosed tumors and the remaining 24 had recurrent brain tumors. Demographics of the evaluable study patients are listed in Table 2.

**Patient Characteristics—Ongoing Expanded LGG Cohort**

From February 2011 and currently ongoing, patients with recurrent or refractory LGG are being recruited from the outpatient clinics at Rady’s Children’s Hospital San Diego and Children’s Healthcare of Atlanta. To date, we have enrolled 6 subjects, aged 2 to 15 years. Two subjects have juvenile pilocytic astrocytoma, 2 have hypothalamic/chiasmatic gliomas, 1 has optic nerve glioma, and 1 has pilomyxoid astrocytoma. A total of 2 of 6 subjects have neurofibromatosis type 1.

**Toxicity—Initial Study**

All 47 patients had no observed dose-limiting toxicities and poly-ICLC was generally very well tolerated. These results are similar to those in previous adult studies demonstrating that patients typically showed fevers of 40°C, myalgia, arthralgia, malaise, nausea, vomiting, and mild elevations of liver enzymes. The overall tally of specific toxicities and maximum grade observed are listed in Table 3 with the numbers in each column representing the number of patients who had that toxicity at any time during study treatment.

One of the children in cohort 2 suffered from grade 3 neutropenia that resolved despite continued therapy. The patient with the neurofibromatosis-associated brain tumor seemed to be very sensitive to poly-ICLC and demonstrated more side effects, including grade 3 fever and elevated transaminases. Elevated transaminases occurred in 6 subjects mainly in cycle 1 and this was thought to be attributable to study drug. When AST/ALT was >4× baseline or grade 4 elevations occurred, poly-ICLC was placed on hold until resolution and then restarted at half the prior dose. All toxicity resolved when drug was held and overall toxicities were minimal.
Tumor Response—Initial Study

Thirty-two patients were evaluable under the response criteria. Positive responses were observed despite the first stage accrual goals not being met for any of the disease strata before study termination. Although there was no statistically significant evidence of efficacy overall, a finding not unexpected given the small size and diversity of the study population, valuable information was acquired in terms of promising clinical responses and trends in the LGG patient subgroup, thereby satisfying the primary phase II objective of acquiring information supporting further, more comprehensive trials. Two patients received poly-ICLC for over 2 years and another subject completed 2 years of planned therapy. We report the following data for each of the 5 study cohorts:

Cohort 1 included patients with recurrent or progressive HGGs (anaplastic astrocytoma or glioblastoma multiforme). It had a total of 16 subjects enrolled with 12 evaluable and 4 ineligible patients. The trial was structured to allow HGG patients, in particular those with glioblastoma multiforme who did not want to get radiotherapy, to receive poly-ICLC upfront. However, all of the HGG patients enrolled on this study were treated in the relapse setting after they received chemotherapy and radiotherapy and had progressive disease. Consequently a number of HGG patients did not survive or remain on study for the duration of 4 weeks required to be considered for response to therapy. Two patients with recurrent anaplastic astrocytoma progressed or died before receiving 4 weeks of poly-ICLC therapy. These were highly refractory recurrent HGG patients.

Of the evaluable patients, a PR was observed in a patient with recurrent anaplastic astrocytoma and this patient received 24 cycles of therapy. Another patient with recurrent HGG had stable disease for >20 months. An additional patient also responded for a total of 3 or 25% response rate. Hence, we conclude that the observed activity may warrant further investigation of poly-ICLC in HGG.

Cohort 2 included patients with recurrent LGGs. The 4 patients with low-grade astrocytoma are the only ones included in the LGG cohort. Long-term responses were seen in 2 of 4 evaluable patients with LGG (50% response rate). These children had a PR followed by stable disease for 18 and 24 months while receiving poly-ICLC after previously documented progression. Both patients had tumors in the midbrain; one an optic nerve glioma, the other a central thalamic neoplasm. Of the 8 patients who did not complete a course of therapy, none had LGG. Two of the 8 patients had undifferentiated malignant brain tumor. From the data we conclude that poly-ICLC has activity in the LGG cohort and is worthy of further study in this disease category. Moreover, the results support more sophisticated molecular profiling of LGG tumor tissue to determine the molecular features that predict sensitivity to this agent in vivo.

Cohort 3 included 13 subjects with newly diagnosed DIPGs who were enrolled after completing radiotherapy. It should be noted for this group that a combination phase II study can be performed with an investigational agent combined with an FDA-approved treatment modality. In this case, due to the poor prognosis of DIPG patients, we were able to get IRB approval to combine poly-ICLC to start immediately after XRT therapy. This cohort was evaluated separately for response and of the 8 patients deemed evaluable, all progressed.
within 2 to 7 months of starting therapy. No tumor responses (CR or PR) were observed and this cohort was closed to patient entry due to a lack of response to the therapy. We concluded that poly-ICLC has no activity in the treatment of childhood DIPGs.

**Cohort 4** included 12 patients with recurrent ependymoma or PNET. No tumor responses were noted in the 7 patients deemed evaluable, but stable disease was observed in 2 of the subjects. The results suggest a lack of activity of poly-ICLC in recurrent ependymoma or PNET.

**Cohort 5** included the single subject with neurofibromatosis, the one who appeared to be very sensitive to poly-ICLC and exhibited considerably greater side effects than the other subjects. The basis for this is not clear but the side effects profile necessitated a lower dosing of poly-ICLC for this subject. This subject had multiple neurofibromas along the spine that were not biopsied.

**Ongoing Expanded LGG Cohort Study—Toxicity and Efficacy**

An interim report on the ongoing phase II trial with the expanded LGG cohort is provided as the study is now at almost 2 years duration and the LGG results are promising. Accrual is slow because the IM route of delivery is a limitation, given the oral biologics available. Nonetheless, we have now enrolled 3 more patients in 3 months and have discussed this trial with a cooperative group, and hence we are confident we will complete the trial. So far patients have all tolerated poly-ICLC therapy well. Two subjects have had stable disease for 18 months, 1 subject has been stable for 6 months, whereas 3 subjects have shown radiologic progressive disease in the follow-up time range. One patient with recurrent optic nerve glioma, worsening visual-field defects, and tumor progression on MRI has responded to poly-ICLC therapy with stable disease for 15 cycles (Fig. 1). Another patient with a suprasellar juvenile pilocytic astrocytoma diagnosed in 2002 initially received treatment with vincristine and carboplatin, and after progression received temozolomide that was stopped due to intolerance. From 2007 until 2011 his tumor continued to progress off therapy and he developed bitemporal hemianopsia. He was started on twice weekly poly-ICLC treatment in July 2011 that he tolerated well. After 3 months of twice weekly poly-ICLC therapy, the patient had MRI changes indicative of tumor microhemorrhage and necrosis. Such changes are indicative of a tumor response as evidenced by findings seen in patients with antiangiogenic therapy. The patient was clinically stable with no changes in vision but was taken off study due to parental withdrawal of consent. Combined with the LGG data from the initial study we can now report that 5 of 10 patients have exhibited long-term stable disease with poly-ICLC therapy.

**DISCUSSION**

This report describes the results of the first prospective pediatric trials of poly-ICLC to assess its toxicity and activity for the treatment of brain tumors. Both the initial study and the expanded LGG cohort phase II trial indicated good tolerability of low-dose poly-ICLC when administered on a 2 d/wk schedule. Three patients in the initial study cohort received the study drug for at least 2 years without complications. The most common side effects also occurred in previous adult trials, and included mild temporary injection site discomfort,
transient fever or malaise, grade 1 or 2 fatigue, nausea, vomiting, and reversible elevations of liver transaminases. These symptoms typically resolved within 1 to 2 weeks. The safety and tolerability of 10 to 50 mcg/kg poly-ICLC is so established for adults that it is used to probe the innate immune response and antiviral effects in healthy volunteers.\textsuperscript{14–16,28} Our pediatric data confirm that there is little concern about the safety of poly-ICLC, and in general it is much better tolerated than standard treatments for pediatric brain tumors.

Although the scale of the initial pilot study precluded the acquisition of formal statistical significance for efficacy, there were clear indications that the LGG patient subgroups may benefit considerably from poly-ICLC treatment. In the ongoing multi-institutional single-arm phase II trial addressing an expanded LGG cohort’s responsiveness to poly-ICLC (clinical trials.gov identifier NCT01188096) there are 2 subjects with stable disease for 18 months, in addition to a subject showing neuroradiographic evidence of intratumoral microhemorrhages and necrosis after only 3 months of poly-ICLC. This is noteworthy as it occurred after years of documented tumor progression. Overall the data from both trials thus far shows that 5 of 10 LGG patients have exhibited a protracted period of stable disease, a result that supports a continuation of the current expanded LGG cohort study and a comparison of the 6-month PFS rate in the expanded cohort study to that of other agent studies in the pediatric LGG population.\textsuperscript{23,24} Interestingly, the initial study revealed a 25\% response rate in HGG and this result may also prompt further investigation. We elected to not pursue HGG presently as we were less confident of identifying potential activity, as the HGG response rate was lower than in LGG (50\%), and the results are based on a small sample and may be further limited by confounding factors such as pseudoprogression.

The response thus far to LGG is encouraging as there was a 50\% response in the initial study, and 3 of 6 patients have stable disease at 6 months of therapy in the expanded cohort study. LGG is a challenge to address in several respects as it often has a varied natural history and a difficult clinical course. Although LGG is comparatively indolent, in some cases these tumors are observed to involute without therapy, whereas others progress despite all available treatment, a situation which also makes the study of this tumor type problematic.\textsuperscript{1} The etiology of LGG is thought to be multifactorial; various genetic, infectious, and immunological factors have been implicated, and the tumors are often infiltrated with leukocytes. Children with LGG such as pilocytic astrocytoma may exhibit altered immune responses, which does suggest that an immunomodulator acting through targets such as TLR3 may potentially provide benefit.\textsuperscript{29}

The efficacy results in our pediatric phase II LGG patients are consistent with several adult studies. One trial with 97 patients found that poly-ICLC may improve the efficacy of chemoradiation and adjuvant TMZ in newly diagnosed glioblastoma, whereas another in 38 adults suggested a possible beneficial effect of poly-ICLC with newly diagnosed and recurrent glioblastoma multiforme and anaplastic astrocytoma.\textsuperscript{30,31} Twenty of the patients receiving at least twice weekly poly-ICLC showed regression or stabilization of tumor on MRI. In another adult study, 5 of 6 young adult patients who had anaplastic astrocytoma but no neurological abnormalities (class 1) were alive and well with a median progression-free follow-up of 61 months versus an expected historical median survival of 59 months on standard radiation/chemotherapy. One hundred percent of patients who received the poly-
ICLC regimen were alive at 2 years versus only 76% who received standard chemotherapy.\textsuperscript{14} Although the foregoing support the effectiveness of poly-ICLC versus standard chemotherapy,\textsuperscript{14} other adult trials have shown that poly-ICLC did not improve progression-free survival in glioblastoma patients.\textsuperscript{15,16} Importantly however, these adult clinical trials did reveal that the LGG subgroup is generally responsive to poly-ICLC, and collectively the adult and our pediatric results do warrant a general effort to achieve further substratification to identify the most responsive LGG patients.

Advances in molecular profiling of brain tumors and the expanding Pediatric Cancer Genome Project have enhanced the understanding of the genetic mutations involved, delineating a risk stratification system for pediatric brain tumors.\textsuperscript{13} In this context the promising results with LGG in our trials justify a determination of whether surrogate markers of tumor response and progression can be identified in pediatric LGG patient serum, peripheral blood mononuclear cells, and/or cerebrospinal fluid. This may allow substratification of the pediatric LGG population and the application of personalized oncologic approach. Moreover, the identification of key biomarkers may facilitate the deciphering of signaling and resistance pathways relevant to poly-ICLC, which may guide the rational combination of poly-ICLC with additional molecular-based therapeutic interventions.\textsuperscript{13} Biomarker analysis is currently underway to determine if poly-ICLC therapy correlates with the regulation of genes involved in the TBK1, interferon and interferon regulatory factors, and the toll-like receptor pathways. Further surrogate markers may also include BRAF-KIAA1549 fusion gene that has predicted favorable outcome in pediatric low-grade astrocytoma, and BRAF-V600E a diagnostic marker for pediatric LGG.\textsuperscript{35-37} Recent whole-genome sequencing of pediatric LGG may provide a further frame work for the identification of informative biomarkers, such as identification of the truncating rearrangements in the MYBL1 transcription factor.\textsuperscript{38}

In summary, the findings of these pediatric phase II trials suggest that poly-ICLC may have activity in the treatment of pediatric LGG, and highlight the potential importance of identifying poly-ICLC responsive LGG patient substrata in the context of personalized therapy. Although positive for LGG, the initial trial was limited in terms of the number of patients, in terms of follow-up, and in terms of technical confounders such as the MRI-based delineation of pseudoprogression from true disease progression. The results obtained thus far need to be verified with more patients enrolled and a longer follow-up period to overcome the limitation of small sample size before positive activity of poly-ICLC in LGG can be confidently declared. Moreover, in terms of biomarkers further prospective randomized studies including multivariate analyses are needed to clearly distinguish between prognostic and predictive effects. If activity of poly-ICLC is confirmed and informed by biomarker analyses, upfront therapy with this agent considering its lack of significant toxicity may be justified in the treatment of LGG.

**Acknowledgments**

Partially supported by award numbers NIH RO1 CA75737 and T32 CA121938 from the National Cancer Institute as well as Moores UCSD Cancer Center Early Clinical Trials Award funded under the Cancer Center Support Grant 5 P30 CA23100-21.
References


FIGURE 1.
Neuroradiographic changes after poly-ICLC treatment in a patient with progressive suprasellar chiasmatic low-grade glioma (indicated by white arrows). Baseline susceptibility weighted imaging (A) and T1-weighted axial (B) and coronal (C–D) postgadolinium sequences. After 3 months of poly-ICLC therapy the tumor showed increased hyperintensity on SWI (E) and on T1-weighted axial (F) and coronal (G–H) postgadolinium sequences consistent with focal areas of microhemorrhage that were not present pretreatment.
### TABLE 1

**Response Criteria**

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>Disappearance of all enhancing tumor, no new lesions, off steroids, neurologically stable or better</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>≥50% reduction in enhancing tumor size, no new lesions, stable or tapering steroid dose, neurologically stable or better</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>The appearance of new lesions or a ≥25% increase in enhancing tumor size for measurable lesions, with or without neurological progression</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>All other situations</td>
</tr>
</tbody>
</table>
### TABLE 2

Baseline Characteristics of 32 Eligible Subjects

<table>
<thead>
<tr>
<th>Diagnosis (n [%])</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade glioma</td>
<td>12 (37.5)</td>
</tr>
<tr>
<td>Astrocytoma, low grade</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Diffuse intrinsic pontine glioma (DIPG)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Primitive neuroectodermal tumor (PNET)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Other brain tumor</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>New or recurrent diagnosis (n [%])</td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed brainstem glioma</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Recurrent brain tumors</td>
<td>24 (75)</td>
</tr>
<tr>
<td>Sex (n [%])</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (53.1)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td>Race (n [%])</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (40.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>14 (43.8)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>Age at study enrollment (y)</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>10.7</td>
</tr>
<tr>
<td>Median age</td>
<td>12.1</td>
</tr>
<tr>
<td>Age range</td>
<td>1.4–20.7</td>
</tr>
</tbody>
</table>

*J Pediatr Hematol Oncol*. Author manuscript; available in PMC 2015 March 11.
## TABLE 3

Total Patient Toxicities by Common Terminology Criteria for Adverse Events (CTCAE) v.3 Toxicity Grade

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar/ataxia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Erythema at injection site</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2</td>
<td>4</td>
<td>16</td>
<td>3</td>
</tr>
</tbody>
</table>