Original Article

Clinical approach to re-irradiation for recurrent diffuse intrinsic pontine glioma

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Abstract

Background: We present our institutional approach for re-irradiation in diffuse intrinsic pontine glioma and their outcomes.

Methods: Consecutive patients of recurrent diffuse intrinsic pontine glioma treated with re-irradiation (January 2015–September 2019) were reviewed retrospectively to describe the clinical-response-based approach followed for the dose and volume decision. Outcomes were defined with clinical and steroid response criteria and survival endpoints included progression-free survival and overall survival as cumulative(c) overall survival and re-irradiation overall survival (re-irradiation starting to death). The Kaplan–Meier method and log-rank test were used for survival analysis.

Results: Twenty-patient cohort with a median (m) age of 7.5 years, m-progression-free survival of 8.4 months and m-Lansky performance score of 50 received re-irradiation of which 17 (85%) were called clinical responders. The median re-irradiation-overall survival with 39.6–41.4, 43.2 and 45 Gy were 5.8, 7 and 5.3 months, respectively. One-month post-re-irradiation steroid independent status was a significant predictor of better survival outcomes (overall survival, P ≤ 0.004). No ≥ grade 3 toxicities were noticed. Two patients succumbed to intra-tumoral hemorrhage.

Conclusions: Higher doses of re-irradiation based on a clinical-response-based approach show improvement in survival and steroid independence rates with acceptable toxicity. Steroid independent status at 1-month post-re-irradiation predicts better outcomes. Prospective studies may validate this with quality of life data.

Key words: re-irradiation, recurrent diffuse intrinsic glioma, clinical-response-based approach, dose-escalation, steroid independence
Introduction

Diffuse intrinsic pontine glioma (DIPG) is an unfortunate diagnosis of childhood which despite treatment has universally fatal outcomes. Historically, several studies have tested various upfront or adjuvant chemotherapy agents, targeted agents alone or in different combinations (1–4) with conventional standard first-line radiotherapy (RT) as well as in salvage setting (5–7) but have failed to demonstrate any meaningful improvement in the outcomes. To date, conventionally fractionated RT to a dose of 54–60 Gray (Gy) remains standard treatment (8), which is essentially a palliative treatment. Median progression-free survival (PFS) and overall survival (OS) in large series and various registry data with adherence to standard diagnostic criteria and standard treatment range from 6–8 to 10–12 months respectively (9–12).

Recently, re-irradiation (reRT) has been demonstrated to be valuable for providing meaningful palliation by alleviating the symptoms and prolonging survival significantly when compared to best supportive care alone (13–22). Patients who responded well with initial RT, as suggested by longer PFS of 6 months or more are the only criteria which may not always simulate with classical DIPG age group. Although collative studies do have more significant numbers (highest 31 patients in pan-European database followed by 16 in Canadian series), they do suffer from heterogeneous patient selection (further clinical deterioration). Steroid response criteria were defined as completely off (CO) (completely weaning off steroids), partially off (PO) (decrease in dosage/frequency or both), persistent need (PN) (persistent need of the same dose per day/unable to taper) and steroid restarted (RS) (described at 1-month post-reRT for patients who were either CO or PO at the end of reRT and later had to be restarted or put on higher doses).

The radiological response was assessed ‘at 1-month post-reRT’. Responses were defined for each patient based on documented details and imaging reports in electronic medical records at the two-time points.

The outcomes were estimated as PFS and OS. PFS was defined from the end of initial RT to the time point of the clinicoradiological consensus of progression as described before. For OS, two-time points were defined as (i) cumulative OS (cOS) from the initial diagnosis to the death; and (ii) reRT OS from reRT starting to the death.

Statistical Package for Social Sciences (SPSS) version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) was used for analysis. Other than descriptive items with rates and percentages, the outcomes were analyzed using the Kaplan–Meier method and log-rank test. The multivariate analysis for relation with various radiotherapy doses was not done due to limited numbers in each bin.

Materials and methods

We retrospectively reviewed the data for all consecutively treated patients of recurrent DIPG with reRT diagnosed from January 2015 to September 2019 at our institution (Institutional Ethics Committee Project No: 900597). The demographic, clinical, treatment and outcome information were retrieved and reviewed from electronic medical records.

The criteria used at our institution for defining progression and suitability for reRT needed the satisfaction of all factors as the following: (i) neurological and steroid response in first RT treatment; (ii) confirmed neurological deterioration status with radiological progression demonstrated on magnetic resonance imaging (MRI) with no leptomeningeal dissemination; (iii) non-resolution of symptoms with dexamethasone; (iv) consensus for findings at multidisciplinary tumor board (included pediatric and adult neuro-oncologist, radiation oncologist, neurosurgeons, pathologist and neuroradiologists). The criteria for neurological deterioration to be termed as progression is the same as standard diagnostic clinical criteria for DIPG. reRT was offered on compassionate grounds only when the progression was established as above with LPS ≥ 40 and a minimum interval of 6 months between initial diagnosis and progression.

When retrospectively reviewed, the reRT dose varied among the cohort. For the ease of understanding, we have clubbed patients who received similar doses and depicted in Figure 1. At our institution, we followed a policy in deciding the total dose for each patient planned for reRT. Patients with diffuse infiltrative disease beyond posterior fossa, but no leptomeningeal dissemination received whole-brain radiation (WBRT) to a dose of 30.6 Gy with 1.8 Gy per fraction. Patients with localized progression limited to posterior fossa only, initially received focal reRT to a dose ranging from 21.6 to 30.6 Gy with 1.8 Gy per fraction. During this, patients who showed clinical improvement (clinical responders), continued reRT till 39–45 Gy with 1.8 Gy per fraction; else (clinical non-responders) were stopped. In the overall cohort, patients treated with reRT (WBRT or focal reRT) and responded clinically in initial 21.6–30.6 Gy were labelled as clinical responders.

For the purpose of this study, clinical and steroid response (to entire treatment) criteria were defined. Responses are reported ‘at the completion of reRT’ and ‘1-month post-reRT’. Clinical response was defined as a very good response (VGR) (complete/near-complete resolution of all neurological signs/symptoms), good response (GR) (partial response in all symptoms), fair response (FR) (partial/complete response in some but not all symptoms), stable response (SR) (no change in any symptom’s severity) and clinical worsening (CW) (further clinical deterioration). Steroid response criteria were defined as completely off (CO) (completely weaning off steroids), partially off (PO) (decrease in dosage/frequency or both), persistent need (PN) (persistent need of the same dose per day/unable to taper) and steroid restarted (RS) (described at 1-month post-reRT for patients who were either CO or PO at the end of reRT and later had to be restarted or put on higher doses).

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Results

Baseline characteristics

A total of 20 eligible patients were identified and included in the study cohort for whom the general characteristics and individual patient characteristics are shown in Table 1 and Supplementary Table 1 respectively. Only three patients were biopsied at initial presentation elsewhere and were not tested for H3K27 mutation due to an inadequate sample. All patients received
index RT to a dose of 54 Gy/30# except in two patients (60 Gy/30#, 54 Gy/27#), resulting in at least GR (VGR in four). Four patients received Temozolomide (TMZ) concurrent with RT, of which three patients continued to receive adjuvant TMZ (6 cycles) as well. Five patients received oral metronomic chemotherapy (Valproate, Etoposide, TMZ and Isotretinoin) as adjuvant therapy post initial RT.

The median PFS post-initial radiotherapy was 8.4 (interquartile range; IQR: 6.6–9.7) months and PFS at 6, 12 and 18 months was 80.2 ± 8.9%, 15 ± 8% and 5 ± 4.9%, respectively, with no patient reaching a PFS up to 2 years. At progression, all patients had at least 2/3 clinical criteria (3/3 in six).

Three patients received second-line chemotherapy at progression and continued to progress, hence they were considered for reRT (patient no 2, 4 and 14, Supplementary Table 1). Two patients were on salvage sodium valproate with no clinical response and were considered for reRT with continued sodium valproate (patient no 7 and 11, Supplementary Table 1). The median interval between the end of the initial RT and the start of reRT was 8.9 (IQR: 7.3–9.9) months. At reRT, the median LPS was 50 (60%: ≤50).

Clinical response to reRT and outcomes
The median cOS for the whole cohort was 16.6 (IQR: 13.9–18.7) months with OS at 12, 18 and 24 months of 95 ± 4.9%, 37.2 ± 11.1% and 15.9 ± 8.4%, respectively. The median reRT OS was 5.5 (IQR: 4.2–6.8) months. Post-reRT, 17 patients had progression; two patients died of intra-tumoral hemorrhage (ITH) and one patient is alive with no signs of re-progression. Of the 17 patients with progression, 16 were confirmed radiologically—12 (60%) were local, four (20%) were disseminated; while the pattern of progression was not known in one patient (5%). There was a significant survival addition of 9.2 months to cOS of 18.1 (95%CI:15.57–20.69) months from PFS of 8.9 (95% CI: 7.35–10.51) months (P < 0.001, Fig. 2) in the whole cohort.

Seventeen (85%) patients were clinical responders with a median cOS of 17.3 (14.7–20.5) months with OS at 12, 18 and 24 months of 100%, 43.9 ± 12.4% and 18.8 ± 9.8%. The median reRT OS was 5.5 (IQR: 4.3–7.3) months.

The clinical responder’s group had continued to have a 100% clinical response rate ‘at the end of reRT’. This included three patients and 14 patients who received WBRT (for extensive disease) and focal reRT (39–45 Gy). Five (including two who received WBRT), five and seven (including one who received WBRT) patients had VGR, GR and FR, respectively. ‘At 1-month post-reRT’, clinical response assessment revealed continued response rate of 76.5% (13/17) with VGR, GR, FR and CW in two, six, five and four patients. The median cOS and reRT OS for patients who received WBRT were 18.3 and 5.3 months, respectively, while those who received focal reRT to a dose of 39–41.4 Gy were 16.3 and 5.9;
Table 1. General characteristics of the study cohort

<table>
<thead>
<tr>
<th>Age—median (IQR)</th>
<th>7.5 years (6–13.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: Female</td>
<td>12:8</td>
</tr>
<tr>
<td>LPS at diagnosis—median (IQR)</td>
<td>70 (50–77.5)</td>
</tr>
<tr>
<td>Clinical diagnostic criteria</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>75% (15 pts)</td>
</tr>
<tr>
<td>Three</td>
<td>23% (5 pts)</td>
</tr>
<tr>
<td>Radiological criteria</td>
<td>100%</td>
</tr>
<tr>
<td>Initial treatment details</td>
<td></td>
</tr>
<tr>
<td>RT dose</td>
<td>54 Gy (19 patients), 60 Gy (one patient)</td>
</tr>
<tr>
<td>Concurrent therapy</td>
<td>20% (4 pts)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>40% (8 pts)</td>
</tr>
<tr>
<td>Median PFS (IQR)</td>
<td>8.4 months (6.6–9.7)</td>
</tr>
<tr>
<td>LPS at reRT—median (IQR)</td>
<td>50 (50–60)</td>
</tr>
<tr>
<td>reRT details</td>
<td>41.4 Gy (33.8–43.2)</td>
</tr>
<tr>
<td>Technique-3DCRT: IMRT</td>
<td>17:3</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>10% (2 pts)</td>
</tr>
<tr>
<td>Salvage therapy</td>
<td>15% (3 pts)</td>
</tr>
<tr>
<td>Pre reRT</td>
<td>5% (1 pt)</td>
</tr>
<tr>
<td>Post reRT</td>
<td>8.9 months (7.3–9.9)</td>
</tr>
</tbody>
</table>

IQR, inter-quartile range; LPS, Lansky performance score; RT, radiotherapy; reRT, re-irradiation; Gy, Gray.

43.2 Gy were 16.6 and 7; and 45 Gy were 16.6 and 5.3 months, respectively (Fig. 1). The different dose levels were not analyzed for any survival difference due to limited numbers in each dose bin. All clinical responders were on steroids at the time of reRT initiation. However, by the end of reRT, seven patients (41.2%) were CO, seven patients (41.2%) were PO and three patients (17.6%) had a PN. ‘At 1-month post-reRT’, the number of CO improved to nine patients (52.9%) while two patients (11.8%) were PO, two patients (11.8%) were PN and four patients (23.5%) were in RS. It was noteworthy that in clinical responder patients who were CO steroids at 1-month post-reRT had significantly longer cOS of 21.80 (95% CI: 17.82–25.78), and reRT OS: 7.06 (95% CI: 5.67–8.44) than who were not: 15.36 (95% CI: 13.85–16.88), P = 0.003 (Fig. 3A) and 4.86 (95% CI: 4.26–5.45), P = 0.004 (Fig. 3B). Radiological response ‘at 1-month post-reRT’ for clinical responders was available for 16 patients, where 14 showed a response and one patient had progression to disseminated disease. Two patients were not included in the radiological response assessment: one patient (patient 7) had ITH on day 7 post-reRT (discussed later) and one patient did not have imaging done.

The three clinical non-responders (Fig. 1, 15%) included patients 1–3 (Supplementary Table 1). ‘At the completion of reRT’, two patients had CW and one patient had SR, while all three had CW ‘1-month post-reRT’. All clinical non-responders had a PN for steroids until they survived. The survival (cOS and reRT OS) per patient in order were 10.6 and 3.2; 12.6 and 4.7; and 16.8 and 6.6 months, respectively.

Toxicity and events

There were no patients documented with > grade 3 acute or late adverse events except for the two patients (patients 7 and 11). Both patients with good clinical improvement post-reRT (FR and GR, respectively) developed ITH on day 7 and 77 post-reRT (10.9 and 11 months from diagnosis), respectively. Both patients had a sudden onset of symptoms; however, clinical deterioration was in the form of persistent headache and vomiting (not responding to steroids) in one patient and sudden onset right-sided weakness in the other patient. Radiological (CT Brain) evaluation revealed features of ITH and was managed conservatively. Unfortunately, both patients succumbed on post-reRT day 84 and 136 respectively. The two patients had received a reRT dose of 43.2 and 45 Gy with reRT, respectively, with concomitant sodium valproate.

Discussion

As per our knowledge, the current series is the second largest after the multi-institutional pan-European SIOP group (International Society of Pediatric Oncology) DIPG study of 31 patients (21), and the largest single institutional experience reported till date. We for the first time present a pragmatic clinical response-based approach for selecting patients to receive higher doses (39.6–45 Gy) of reRT. We also reasonably demonstrate an acceptable balance of safety/toxicity with clinical and steroid outcomes at these reRT doses.

In a systematic review (18), the benefit of re-RT was reviewed from five prominent studies and found that there was a statistically significant median survival gain of 3–4 months with reRT doses ranging from 18 to 36 Gy. The three most extensive series using reRT doses of 18–20, 19.8–30 and 21.6–36 Gy showed median OS benefit of 2.7, 3.4 and 4.1, respectively, suggesting a reRT dose–response relationship (19–21). In our study, we used 20–45 Gy achieving post-reRT OS of 4.4 months suggesting a linear dose–response benefit. In a subpopulation of our cohort, the dose bins from 39.6–41.4 to 43.2–45 Gy showed median post-reRT OS of 4.8, 5.8 and 4.1 months further strengthening the belief in the existence of dose–response curve at least till 43.2 Gy. Although due to the very small sample size per dose bin, further statistical analysis could not be conducted.

A recently published meta-analysis of seven studies with 90 patient’s cohort included the bulk of its patients from the above studies and the same dose range (20–36 Gy) suggested median OS
post-reRT of 6.2 months (17). It is noteworthy that only 56 (62%) patients of limited studies were considered for the survival analysis where median PFS post initial RT was 11–14 months and cOS was reported as 16.4 months (17). In our study, the median PFS post initial RT was 8.4 months with cOS of 16.6 months. Comparing these numbers, the OS benefit expressed in the meta-analysis does not match with ours, despite having slightly lower initial PFS and similar cOS. This may be due to inherent issues with meta-analysis studies where studies with very small sample size, variable case selection and variable/heterogeneous definitions of endpoint are pooled together. These issues are common with multi-institutional series of rare conditions like reRT in DIPG. Variable case selection refers to the inclusion of patients with atypical characteristics such as older age of diagnosis, longer latency of diagnostic symptoms and longer than usual initial PFS (19,21). These issues make a direct correlation or comparison between studies at times very complicated.

In DIPG, steroids are widely used in the waiting period for initial or reRT and supportive or end of life management. RT has been established to reduce steroid dependency at the primary setting, and now lately at reRT setting as well (15,16,19,20). In the meta-analysis, four studies with 42 patients (<50%) were included to study the pattern of steroid use suggesting complete weaning off rates of 76% (95% CI,38–100%) (17). Of these four studies, the most extensive series (16 patients) where explicit data are presented in the public domain, reported weaning of dexamethasone by the end of reRT in 56% (19). In the present study, the steroid weaning rates (CO) in responders were 41.2% at the end of reRT and increased to 52.9% at 1-month post-reRT. In our study, we additionally demonstrate the predictive value of steroid weaning off rates at 1-month post-reRT for survival outcomes.

As there was no >grade 3 toxicity witnessed, we would like to suggest dose-escalation to 43 Gy may be safe post initial 54 Gy in classical DIPG patients with initial PFS of >6 months and showing clinical response in first 10–15 fractions of reRT. Although, ITH can occur as a part of natural history in DIPG with increasing rates with longer survival. It is estimated that the cumulative incidence of symptomatic ITH increases from 6 months to 12 months’ survivors as 8.9% ± 4%–17.8 ± 6%, respectively (23). The authors do not believe that incident ITH in two of our patients is directly related to dose escalation in reRT but cannot also exclude the relatedness to reRT or reRT dose or concurrent use of sodium valproate, hence due caution is suggested for the highest dose bin of 45 Gy.

Ideally, a prospective phase II dose-escalating protocols should be performed with a standardized assessment of clinical/neurological response, steroid dependency and toxicity reporting. To date, only one prospective dose-finding study has been reported using a utility-analysis-based model to differentiate between 24, 26.4 and 30.8 Gy (13). There are several critiques of the conclusions of the study as addressed elsewhere (24,25) but notably the current study and several other large series demonstrate reasonable evidence for safety with higher doses (19,20). Currently, an ongoing multi-institutional prospective Canadian study with 25 patients is testing doses of 30.6 and 36 Gy (NCT03126266). Till more robust dose outcome relationships and safety data emerge, variant practice will be seen across the centres.

As per WHO 2017 update, DIPG forms a part of a much wider entity ‘diffuse midline glioma’ sharing similar molecular subtypes of ‘H3K27M’ having dismal outcomes posing challenging clinical situation at progression (28). Our study cohort may help clinicians offer a similar approach to clinical response-based reRT treatments in other diffuse midline gliomas as well.

There are several limitations of our study, of which retrospective nature and limited sample size being the most critical. We have demonstrated the benefit with reRT in a cohort of 20 patients, though our study lacks a control group in whom reRT was not instituted at progression. However, it is well known in literature including data from our institution, to say that the outcomes are dismal in recurrent DIPG with who do not receive reRT (2–3 months) (16,19,27). Further, there is a lacuna of meticulous steroid use reporting after 1-month post-reRT, asymptomatic radiation necrosis rates at higher

Figure 3. Impact of steroid dependency on cumulative overall survival (A), re-irradiation survival (reRT OS) (B).
dose and quality of life data are not available. At our institute, most patients are outstated from far off places and due to logistic reasons we do not recommend systematic three monthly MRIs in post palliative intent treatments. The 1-month post-reRT MRI reporting for radiation necrosis can be very tricky and unreliable. Again, due to far off patient’s poor access to immediate higher medical care, we sometimes have a higher threshold to wean off completely and a lower threshold for restarting steroids when compared to western practice (26). Although we have reported the data regarding the use of any concurrent/adjuvant or salvage medical agents, the bias against their benefit/harm cannot be addressed. Even though this is one of the largest reRT series, we do not have adequate numbers in each dose bins to statistically demonstrate the dose–response relationship.

Radiotherapy in DIPG is always palliative whether in the first or second instance, and authors feel that decision on dose should be based on previous institutional experience, expected benefit and toxicity, and in concurrent and elaborate discussion between family and physician and not limited to the length of treatment or logistics. In the current study, the outcomes with the pragmatic clinical response-based approach are shown, suggesting safety and improved outcomes with a higher dose from 39.6 to 45 Gy. The dose of 43 Gy seems to bring the best outcomes and the predictive value of steroid weaning off rates at 1-month post-reRT needs further exploration.

Supplementary Material
Supplementary material is available at Japanese Journal of Clinical Oncology online.

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Conflict of interest statement
None declared.

Ethics Approval
IEC approval was obtained for the retrospective study.

Consent to participate
As this was a retrospective study, consent was waived off by IEC.

Consent for publication
Not applicable.

Availability of data and material
All data and materials as well as software application or custom code support their published claims and comply with field standards.

Author contributions
All authors have contributed to the conception of the work, acquisition, analysis and interpretation of the data.

Concise messages
• reRT significantly improves survival and steroid dependence.
• A clinical response-based approach for dose and volume decision described.
• reRT dose of 39–45 Gy can be safely used with good salvage outcomes.
• Steroid independent status at 1-month post-reRT as a predictor of better outcomes.

References


