

Letter to the Editor

5-Azacitidine in patients with *IDH1/2*-mutant recurrent glioma

Mutations of isocitrate dehydrogenase genes (*IDH1* or *IDH2*) are found in approximately 40% of gliomas. While *IDH1/2* mutations are associated with improved outcomes in gliomas,¹ very few second-line therapies exist for patients relapsing following standard-of-care surgery, ie, radiotherapy and chemotherapy. It was hypothesized that *IDH1/2*-mutant glioma patients might benefit from treatment with DNA methyltransferase (DNMT) inhibitors, since *IDH1/2*-mutant cancers often exhibit extensive DNA hypermethylation in cytosine-phosphate-guanine (CpG)-rich domains (CpG island methylated phenotype [CIMP]), which is associated with altered gene expression and increased tumor cell proliferation.^{2,3} In *IDH1/2*-mutant glioma preclinical models, treatment with DNMT inhibitors reduces DNA methylation of promoter loci of genes involved in glial differentiation and inhibits tumor growth.^{4,5} However, it remains unknown whether patients with *IDH1/2*-mutated glioma might respond to DNMT inhibitors. 5-Azacitidine is a DNMT inhibitor currently approved for the treatment of high-risk myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).^{6,7} Among patients with AML, one study reported better response to DNMT inhibitors in *IDH1/2*-mutated patients,⁸ albeit these results were not consistent with other series.^{9,10} In this case series, we evaluated the safety and efficacy of 5-azacitidine in *IDH1/2*-mutant recurrent gliomas.

Twelve glioma patients were treated with 5-azacitidine between May 2014 and December 2016 through an institutionally approved expanded access application (Table 1). Patients were eligible if they had an *IDH1/2*-mutant recurrent glioma and provided informed consent to participate. We disclosed information on the potential risks and benefits of azacitidine treatment by providing a written document to patients. Seven (58.3%) patients had an *IDH1*-mutant astrocytoma (1 World Health Organization grade IV, 4 grade III, 2 grade II), and 5 patients (41.7%) had an *IDH1*-mutant, 1p/19q codeleted oligodendroglioma (3 grade III and 2 grade II). The cohort represented a heavily pretreated population with a median of 3 prior systemic therapies (range, 2–5). 5-Azacitidine dosing was based on prior MDS and AML studies.^{6,7} Patients received a median of 6 cycles of 5-azacitidine (range, 1–27) with a median therapeutic intensity of 90% (range, 75–100). Three (25%) patients received concomitant bevacizumab (10 mg/kg q2 wk). Adverse events observed in this population were consistent with the toxicity profile of 5-azacitidine in AML and were manageable (Supplementary Table 1).⁶ The most common adverse event

leading to dose reduction was grades 3–4 neutropenia in 9 patients (75%), of whom 7 received concomitant granulocyte colony stimulating factor (G-CSF) injections during the following cycles. Patients who experienced grade 3 or 4 toxicities had reduction in the total number of treatment days per cycle (5 instead of 7 days) or delay in the next cycle of 5-azacitidine. No blood transfusions were necessary.

At last follow-up (median duration, 20.0 mo; range, 1.2–33.3), all 12 patients had progressed. No patient achieved a radiographic response. Five (41.7%) had disease stabilization as best response, of whom 2 (16.7%) had disease stabilization for more than 18 months. One patient with a grade III astrocytoma (*IDH1*-mutant, 1p/19q non-codeleted, p16 deleted) previously treated with temozolomide, procarbazine/CCNU/vincristine (PCV), and radiation therapy, had a sustained decrease in tumor enhancement with single-agent 5-azacitidine, which lasted for 21 months (Supplementary Figure 1). In addition, one patient with a grade III oligodendroglioma (*IDH1*-mutant, 1p/19q codeleted, p16 wild-type) previously treated with radiation therapy, temozolomide, and PCV had a sustained stabilization for 22 cycles with single-agent 5-azacitidine. The median progression-free survival (PFS) was 4.7 months (95% CI: 2.1–7.4), and the median OS was 25.2 months (95% CI: 4.0–30.5) (Supplementary Figure 2A, B). Patients who had received prior treatment with bevacizumab had shorter PFS than patients with no prior bevacizumab (median PFS, 1.0 [95% CI: 1.0–1.3] vs 21.7 [95% CI: 5.0–23.7], $P = 0.004$) (Supplementary Figure 2C, D).

While preclinical data suggest that patients with *IDH1/2*-mutant gliomas might benefit from DNMT inhibitors,^{4,5} we observed minimal efficacy of 5-azacitidine in this heavily pretreated population. Of note, 2 patients achieved long-lasting disease stabilization, and 1 patient had a sustained decrease in tumor enhancement. This finding suggests that a subset of patients with *IDH1/2*-mutated gliomas might benefit from treatment with DNMT inhibitors. We observed that patients with large and rapidly progressing tumors who received prior treatment with bevacizumab had shorter PFS and OS, which might be explained by a more advanced disease stage in this subset of patients. In addition, data from AML patients showed that 5-azacitidine is less efficient in rapidly proliferative diseases and that a subset of patients can have delayed response to 5-azacitidine (median time to first response of 2 cycles [range, 1–16 cycles] in the AZA-001 trial),⁶ overall suggesting that patients with relatively slow-growing tumors might be better candidates for treatment with 5-azacitidine. Beside identifying patients more likely to benefit from DNMT inhibitors, recent preclinical studies showed that 5-azacitidine can enhance the therapeutic effect of the alkylating agent temozolomide in xenograft models of *IDH1/2*-mutant gliomas.⁵ This suggests that combination of

Table 1. Clinical, histologic, and molecular characteristics of the patients treated with 5-azacitidine

Characteristic	n = 12
Sex, no. (%)	
Male	8 (66.7)
Female	4 (33.3)
Age at baseline, median (range)	43.5 (29–69)
KPS at baseline, median (range)	70 (50–80)
Histomolecular subgroup, no. (%)	
Oligodendroglioma, 1p/19q codeleted, IDH1-mutant	5 (41.7)
Astrocytoma, IDH1-mutant	7 (58.3)
Tumor grade, no. (%) [†]	
Grade II	4 (33.3)
Grade III	7 (58.3)
Grade IV	1 (8.3)
p16 status, no. (%)	
Normal	7 (58.3)
Deleted	5 (41.7)
Number of prior surgery, median (range)	2 (1–4)
Prior radiation therapy, no. (%)	
Yes	10 (83.3)
No	2 (16.7)
Prior systemic therapy, no. (%)	
Temozolomide	12 (100.0)
PCV	11 (16.7)
Carmustine (BCNU)	1 (8.3)
Carboplatin	2 (16.7)
Bevacizumab	4 (33.3)
Number of prior systemic therapies, median (range)	3 (2–5)
Steroid treatment at baseline, no. (%)	4 (36.4)*

[†]Median delay between last surgery and azacitidine treatment: 63.8 mo (range, 7.5–165.4).

*Data not available for one patient.

5-azacitidine with DNA damaging agents might enhance the therapeutic effect of DNMT inhibitors in this population. Our study is mainly limited by the small sample size, patients' heterogeneity, and concomitant use of bevacizumab in a subset of patients. However, we believe that the evidence generated in this case series will inform the design of trials evaluating DNMT inhibitors in patients with *IDH1/2*-mutant gliomas. In conclusion, this report represents the first clinical experience with DNMT inhibitors in gliomas, and shows that 5-azacitidine has a manageable toxicity profile in this population and possible antitumor activity in a subset of patients. Further evidence from ongoing prospective trials is warranted to conclude on the efficacy of 5-azacitidine in this disease (NCT02223052, NCT02332889).

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Funding

MT was supported by Fondation pour la Recherche Médicale (FDM 41635). There is no other relevant funding information.

Acknowledgments

The authors would like to thank the patients who took part in the study and their families, as well as the staff, research coordinators, and investigators at each participating institution. The authors would like to acknowledge the ICM Genotyping and Sequencing Core Facility (IGENSEQ) for sharing expertise related to analysis of copy array and sequencing data.

Conflict of interest statement. FB reports employment from Celgene (I); stocks from Crossject (I); research grants from Sanofi, outside the submitted work. KHX reports advisory board honoraria from Bristol-Myers Squibb, outside the submitted work. AI reports travel funding from Carthera, and personal fees from BMS, Hoffmann-La Roche, and Cipla (certified continuing education), outside the submitted work. MS reports an advisory board for Taiho oncology and Genenta, and travel grants from Abbvie. MT reports consulting or advisory role from Agios Pharmaceutical, Integragen, and Taiho Oncology, outside the submitted work; travel, accommodations, expenses from Merck Sharp & Dohme, outside the submitted work. The other authors report no disclosures.

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