Neuro-Oncology
23(1), 167–168, 2021 | doi:10.1093/neuonc/noaa227 | Advance Access date 16 October 2020

Letter to the Editor

Management of gliomas in patients with Lynch syndrome

Lynch syndrome (LS) is an inherited condition of defective DNA mismatch repair (MMR). LS is caused by autosomal dominant heterozygous germline mutations in one of 4 MMR genes: mutL homologue 1 (MLH1), mutS homologue 2 (MSH2), mutS homologue 6 (MSH6), and postmeiotic segregation increased 2 (PMS2). Individuals with LS are primarily predisposed to gastrointestinal and endometrial but also other cancers, including astrocytomas and oligodendrogliomas (although the literature lacks documented reports of 1p/19q codeletion specifically in this cohort).[1,2]

The MMR system repairs base-pair mismatches that are generated by errors in base pairing during DNA replication.[3] Patients with LS have a germline mutation in one allele of a MMR gene but require a somatic inactivation of the remaining wild-type allele in order for cancers to develop.[4] Constitutional mismatch repair deficiency syndrome, on the other hand, results from biallelic germline mutations in one of the 4 MMR genes.[5] Ultimately, biallelic inactivation of MMR genes causes an increased mutation rate leading to a hypermutator phenotype which is characteristic of MMR deficient tumors. In addition, polymorphisms accumulate within the microsatellite repeat regions due to DNA polymerase slippage events leading to microsatellite instability (MSI).

Temozolomide (TMZ)—an alkylating agent—is a standard option in the treatment of gliomas. TMZ induces DNA damage by methylating the N^7 and O^6 positions of guanine and the N^3 position of adenine. O^6 DNA-methylation is highly mutagenic and induces a futile mismatch repair cycle generating lethal double-strand breaks leading to checkpoint activation and apoptosis.[4]

Given the dependence on functional mismatch repair for the efficacy of TMZ and other alkylating agents,[6] MMR-deficient cells are inherently more resistant to their cytotoxic effects and may survive at the cost of extensive mutagenesis.[7,8] Recently, glioma patient-derived cell lines with CRISPR–Cas9 mediated knockout of MSH2, MSH6, MLH1 or PMS2 showed resistance to TMZ, a monofunctional alkylator but not to lomustine (CCNU), a bifunctional alkylating agent.[9] Similarly, loss of MMR function has been observed in recurrent glioblastomas following treatment with TMZ primarily by inactivation of MSH6 leading to treatment resistance.[10,11] The role of MMR in the cytotoxicity of ionizing radiation is less well understood and may depend on the dose of radiation.[6,12] However, risks should be weighed against benefits from treatment in patients with LS given the theoretical risk of secondary malignancies.[13]

The base excision repair (BER) pathway is important in the repair of DNA damage at the N^3-adenine and N^7-guanine base lesions. The DNA repair enzyme, poly(ADP-ribose) polymerase (PARP) has an important role in the proper repair of single-strand DNA breaks that are generated during BER.[14] PARP inhibitors have been tested for their ability to enhance the activity of TMZ. The effect was most pronounced in MMR-deficient cells, which are generally resistant to the effects of TMZ as discussed above.[7] In fact, recent data suggest resensitization of MSH6-inactivated, MMR-deficient glioblastoma cells with combination treatment of PARP inhibitors plus TMZ.[15]

While LS in not routinely screened for in clinical practice, strong family history of relevant cancers, personal history of more than one cancer, or an incidental finding of one of the LS mutations when sequencing gliomas suggest the need for referral to genetic counseling. The above data raises concerns about using the standard of care regimen including TMZ when treating patients with LS and gliomas. Rather, the use of CCNU or a combination of TMZ plus PARP inhibition have a stronger biological rationale. The concern also applies to procarbazine when using procarbazine, CCNU and vincristine (the PCV regimen) for oligodendrogliomas.[14] Furthermore, the use of immune checkpoint inhibitors is now approved by the FDA for solid tumors with MSI or MMR deficiency and is an option for LS glioma patients. However, more research is needed as it was interestingly noted that MSI may not be always present in MMR-deficient gliomas[9] and initial case series suggest lack of efficacy of immunotherapy in recurrent MMR-deficient gliomas.[9,16] A clinical trial is ongoing NCT02359565.

Funding

This study did not receive any funding.

Conflict of interest statement. The authors have no conflicts of interest pertaining to this study.

Iyad Alnahhas, Appaji Rayi, Shirley Ong, Pierre Giglio, and Vinay Puduvalli

Division of Neuro-Oncology, Department of Neurology, Thomas Jefferson University, Philadelphia, Pennsylvania (I.A.); Department of Neurology, Charleston Area Medical Center, Charleston, West Virginia (A.R.); Division of Neuro-Oncology, Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, Ohio (S.O., P.G., V.P.)

Corresponding Author: Iyad Alnahhas, MD, MSc., 901 Walnut St. Room 310G, Philadelphia, PA, 19107 (iyad.alnahhas@gmail.com).

This study has not been previously presented or published.

References

1. Rice T, Lachance DH, Molinaro AM, et al. Understanding inherited genetic risk of adult glioma—a review. *Neurooncol Pract.* 2016;3(1):10–16.
2. Therkildsen C, Ladelund S, Rambech E, Persson A, Petersen A, Nilbert M. Glioblastomas, astrocytomas and oligodendrogliomas linked to Lynch syndrome. *Eur J Neurol.* 2015;22(4):717–724.
3. Kunkel TA, Erie DA. DNA mismatch repair. *Annu Rev Biochem.* 2005;74:681–710.
4. Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of Lynch syndrome: 1895-2015. *Nat Rev Cancer.* 2015;15(3):181–194.
5. Wimmer K, Kratz CP, Vasen HF, et al; EU-Consortium Care for CMMRD (C4CMMRD). Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). *J Med Genet.* 2014;51(6):355–365.
6. Stojic L, Brun R, Jiricny J. Mismatch repair and DNA damage signalling. *DNA Repair (Amst).* 2004;3(8-9):1091–1101.
7. Heinen CD. Translating mismatch repair mechanism into cancer care. *Curr Drug Targets.* 2014;15(1):53–64.
8. Jiricny J. The multifaceted mismatch-repair system. *Nat Rev Mol Cell Biol.* 2006;7(5):335–346.
9. Touat M, Li YY, Boynton AN, et al. Mechanisms and therapeutic implications of hypermutation in gliomas. *Nature.* 2020;580(7804):517–523.
10. Cahill DP, Levine KK, Betensky RA, et al. Loss of the mismatch repair protein MSH6 in human glioblastomas is associated with tumor progression during temozolomide treatment. *Clin Cancer Res.* 2007;13(7):2038–2045.
11. Yip S, Miao J, Cahill DP, et al. MSH6 mutations arise in glioblastomas during temozolomide therapy and mediate temozolomide resistance. *Clin Cancer Res.* 2009;15(14):4622–4629.
12. Martin LM, Marples B, Coffey M, et al. DNA mismatch repair and the DNA damage response to ionizing radiation: making sense of apparently conflicting data. *Cancer Treat Rev.* 2010;36(7):518–527.
13. Wojciechowicz K, Cantelli E, Gerwen BV, et al. Temozolomide increases the number of mismatch repair–deficient intestinal crypts and accelerates tumorigenesis in a mouse model of Lynch syndrome. *Gastroenterology.* 2014;147(5):1064–72.e5.
14. Fu D, Calvo JA, Samson LD. Balancing repair and tolerance of DNA damage caused by alkylating agents. *Nat Rev Cancer.* 2012;12(2):104–120.
15. Higuchi F, Nagashima H, Ning J, Koerner MVA, Wakimoto H, Cahill DP. Restoration of temozolomide sensitivity by parp inhibitors in mismatch repair deficient glioblastoma is independent of base excision repair. *Clin Cancer Res.* 2020;26(7):1690–1699.
16. Ahmad H, Fadul CE, Schiff D, Purow B. Checkpoint inhibitor failure in hypermutated and mismatch repair-mutated recurrent high-grade gliomas. *Neurooncol Pract.* 2019;6(6):424–427.