

1-30-2021

Management of gliomas in patients with Lynch syndrome.

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Recommended Citation

Alnahhas, Iyad; Rayi, Appaji; Ong, Shirley; Giglio, Pierre; and Puduvalli, Vinay, "Management of gliomas in patients with Lynch syndrome." (2021). *Department of Neurology Faculty Papers*. Paper 239.

<https://jdc.jefferson.edu/neurologyfp/239>

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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 four 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 1p19q co-deletion 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 four 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 N⁷ and O⁶ positions of guanine and the N³ position of adenine. O⁶DNA-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 temozolomide, 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 N³-adenine and N⁷-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 temozolomide as discussed above ⁷. In fact, recent data suggests resensitization of MSH6-inactivated, MMR-deficient glioblastoma cells with combination treatment of PARP inhibitors plus temozolomide ¹⁵.

While LS is 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 gliomas⁹ and initial case series suggest lack of efficacy of immunotherapy in recurrent MMR-deficient gliomas^{9,16}. A clinical trial is ongoing NCT02359565.

References:

1. Rice T, Lachance DH, Molinaro AM, Eckel-Passow JE, Walsh KM, Barnholtz-Sloan J, et al. Understanding inherited genetic risk of adult glioma – a review. *Neuro-Oncology Practice*. 2016;3(1):10-6.
2. C. Therkildsen, S. Ladelund, E. Rambech, A. Persson, A. Petersen, M. Nilbert. Glioblastomas, astrocytomas and oligodendrogliomas linked to Lynch syndrome. *European Journal of Neurology*. 2015;22(4):717-24.
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):181-94.
5. Wimmer K, Kratz CP, Vasen HF, Caron O, Colas C, Entz-Werle N, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). *J Med Genet*. 2014;51(6):355-65.
6. Stojic L, Brun R, Jiricny J. Mismatch repair and DNA damage signalling. *DNA Repair (Amst)*. 2004;3(8-9):1091-101.
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):335-46.
9. Touat M, Li YY, Boynton AN, Spurr LF, Iorgulescu JB, Bohrsen CL, et al. Mechanisms and therapeutic implications of hypermutation in gliomas. *Nature*. 2020;580(7804):517-23.
10. Cahill DP, Levine KK, Betensky RA, Codd PJ, Romany CA, Reavie LB, 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):2038-45.
11. Yip S, Miao J, Cahill DP, Iafrate AJ, Aldape K, Nutt CL, et al. MSH6 mutations arise in glioblastomas during temozolomide therapy and mediate temozolomide resistance. *Clinical cancer research*. 2009;15(14):4622-9.
12. M. Martin L, Brian Marples, Mary Coffey, Mark Lawler, H. Lynch T, Donal Hollywood, et al. DNA mismatch repair and the DNA damage response to ionizing radiation: Making sense of apparently conflicting data. *Cancer Treatment Reviews*. 2010;36(7):518-27.
13. Kamila Wojciechowicz, Erika Cantelli, Gerwen Bastiaan V, Mirjam Plug, Wal Anja VD, Elly Delzenne-Goette, 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. *Nature Reviews Cancer*. 2012;12(2):104-20.
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):1690-9.
16. Ahmad H, Fadul CE, Schiff D, Purow B. Checkpoint inhibitor failure in hypermutated and mismatch repair-mutated recurrent high-grade gliomas. *Neuro-Oncology Practice*. 2019;6(6):424-7.