Temozolomide Hepatotoxicity

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Serum transaminase elevations occur during temozolomide therapy in up to 12% of patients, but these elevations are usually mild and self-limited, not requiring dose adjustment or drug discontinuation [1].

A close monitoring of liver function tests is recommended during treatment with temozolomide [2] [3] [4].

Temozolomide hepatotoxicity although infrequent, can necessitate interruption of cancer chemotherapy and cause significant debility in already compromised patients [5].

Case reports

A 65-year-old patient with glioblastoma multiforme (Glioblastoma) has been treated with radiochemotherapy including temozolomide (TMZ) after surgery. The treatment outcome was evaluated as stable disease with a tendency to slow tumor progression. In addition to standard medication (ondansetron, valproic acid, levetiracetam, lorazepam, clobazam), the patient took the antimalarial drug artesunate (ART) and a decoction of Chinese herbs (Coptis chinensis, Siegesbeckia orientalis, Artemisia scoparia, Dictamnus dasycarpus). In consequence, the clinical status deteriorated. Elevated liver enzymes were noted with peak values of 238 U/L (GPT/ALAT), 226 U/L (GOT/ASAT), and 347 U/L (γ-GT), respectively. After cessation of ART and Chinese herbs, the values returned back to normal and the patient felt well again. In the literature, hepatotoxicity is well documented for TMZ, but is very rare for ART. Among the Chinese herbs used, Dictamnus dasycarpus has been reported to induce liver injury. Additional medication included valproic acid and levetiracetam, which are also reported to exert hepatotoxicity. While all drugs alone may bear a minor risk for hepatotoxicity, the combination treatment might have caused increased liver enzyme activities. It can be speculated that the combination of these drugs caused liver injury. We conclude that the compassionate use of ART and Chinese herbs is not recommended during standard radiochemotherapy with TMZ for Glioblastoma [6].

Grieco et al. published a case of severe temozolomide-induced liver disease during concurrent radiotherapy treatment, at a dose level of 75 mg/m2 [7].

A 62-year female received radiotherapy over six weeks with daily 75 mg/m2 Temozolomide (TMZ) for Glioblastoma (GB). At the last week of radiotherapy, her liver enzymes and serum bilirubin started deteriorating. TMZ was discontinued. The histopathology demonstrated the features of acute cholestasis and focal parenchymal inflammation. A range of investigations failed to show any other

contributory cause of hepatitis. She required in-hospital care for a prolonged period for a grade three hepatic failure. The liver functions very slowly recovered over 40 weeks, but her general condition continues to deteriorate. TMZ may cause a mild temporary rise in the liver enzymes and has been reported to reactivate hepatitis B. In few other cases concomitant medications were the possible causes of hepatitis. However, searching the Medline and other bibliographic database, we have not come across any case of TMZ-induced liver injury (TMZ-DILI). Histopathology and pattern of liver enzyme elevation suggest that unlike Dacarbazine, which causes veno-occlusive type liver damage, TMZ in this patient caused mainly cholestasis type liver injury. On Naranjo Adverse Drug Reaction (ADR) probability scale, this case falls in probable grade (Scale 7) [8)]

Melchardt et al. reported the case of severe liver toxicity with jaundice during radiochemotherapy with temozolomide likely due to interaction with a popular Chinese herbal formula after surgery for glioblastoma. After cessation of the herbal formula as well as the chemotherapy liver enzymes slowly normalized. Due to tumor progression the patient was retreated with temozolomide for 5 cycles without toxicity. Because of further progression combination treatment of bevacizumab and irinotecan was started and again no liver toxicity was observed

They concluded that the observed toxicity with jaundice was probably caused by an interaction of this popular Chinese formula and temozolomide. This is the first report about a relevant interaction of temozolomide and any herbal formula. [9)].

Sarganas et al. reported a patient diagnosed with Glioblastoma who developed severe sustained cholestatic hepatitis following treatment with TZM. The cholestasis was not reversible after withdrawal of TZM during 6 months before the patient's death. Another 2 published case reports of sustained cholestasis following TZM treatment were identified; however, the sustained nature of cholestasis was not emphasized in these reports. Sixteen cases of cholestatic hepatitis/cholestasis associated with TZM were identified in the FDA spontaneous reporting system between 2007 and 2010. Information on the course of the cholestasis in these cases could not be retrieved. In the literature there are other published reports of hepatotoxicity associated with TZM that have reported reversibility upon withdrawal of the drug. Thus, TZM appears to cause different types of hepatotoxicity. Particular attention should be paid to sustained cholestasis as a very serious type of TZM-associated liver toxicity [10)].

Hepatitis B virus reactivation during temozolomide administration

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References

1)
https://www.ncbi.nlm.nih.gov/books/NBK548816/#:~:text=embryo%2Dfetal%20toxicity.-,Hepatotoxicity,dose%20adjustment%20or%20drug%20discontinuation.
2) , 7)
Grieco A, Tafuri MA, Biolato M, Diletto B, Di Napoli N, Balducci N, Vecchio FM, Miele L. Severe cholestatic hepatitis due to temozolomide: an adverse drug effect to keep in mind. Case report and

review of literature. Medicine (Baltimore). 2015 Mar;94(12):e476. doi: 10.1097/MD.0000000000000476. PMID: 25816026; PMCID: PMC4554001.
3)

Niewald M, Berdel C, Fleckenstein J, Licht N, Ketter R, Rübe C. Toxicity after radiochemotherapy for glioblastoma using temozolomide–a retrospective evaluation. Radiat Oncol. 2011 Oct 21;6:141. doi: 10.1186/1748-717X-6-141. PMID: 22017800; PMCID: PMC3213071.
4)

Goldbecker A, Tryc AB, Raab P, Worthmann H, Herrmann J, Weissenborn K. Hepatic encephalopathy after treatment with temozolomide. J Neurooncol. 2011 May;103(1):163-6. doi: 10.1007/s11060-010-0354-y. Epub 2010 Aug 22. PMID: 20730617.
5)

Grant LM, Kleiner DE, Conjeevaram HS, Vuppalanchi R, Lee WM. Clinical and histological features of idiosyncratic acute liver injury caused by temozolomide. Dig Dis Sci. 2013 May;58(5):1415-21. doi: 10.1007/s10620-012-2493-9. Epub 2012 Dec 5. PMID: 23212393; PMCID: PMC3826911.
6)

Efferth T, Schöttler U, Krishna S, Schmiedek P, Wenz F, Giordano FA. Hepatotoxicity by combination treatment of temozolomide, artesunate and Chinese herbs in a glioblastoma multiforme patient: case report review of the literature. Arch Toxicol. 2017 Apr;91(4):1833-1846. doi: 10.1007/s00204-016-1810-z. Epub 2016 Aug 12. PMID: 27519711.
8)

Dixit S, Hingorani M, Afzal P, Campbell AP. Temozolomide induced liver injury. Acta Neurol Belg. 2011 Sep;111(3):249-51. PMID: 22141295.
9)

Melchardt T, Magnes T, Weiss L, Grundbichler M, Strasser M, Hufnagl C, Moik M, Greil R, Egle A. Liver toxicity during temozolomide chemotherapy caused by Chinese herbs. BMC Complement Altern Med. 2014 Mar 30;14:115. doi: 10.1186/1472-6882-14-115. PMID: 24679099; PMCID: PMC3994275.
10)

Sarganas G, Orzechowski HD, Klimpel A, Thomae M, Kauffmann W, Herbst H, Bronder E, Garbe E. Severe sustained cholestatic hepatitis following temozolomide in a patient with glioblastoma multiforme: case study and review of data from the FDA adverse event reporting system. Neuro Oncol. 2012 May;14(5):541-6. doi: 10.1093/neuonc/nos056. Epub 2012 Mar 6. PMID: 22394496; PMCID: PMC3337307.