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Pharmacokinetics of temozolomide in association with fotemustine in malignant melanoma and malignant glioma patients: comparison of oral, intravenous, and hepatic intra-arterial administration.

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Abstract

PURPOSE: Depletion of the DNA repair enzyme O6-alkylguanine-DNA alkyltransferase (AT) has been shown to increase tumor sensitivity to chloroethylnitrosoureas. Temozolomide (TMZ), an analogue of dacarbazine, can deplete AT, suggesting that it may be used to sensitize tumors to chloroethylnitrosoureas. However, the influence of nitrosoureas on the pharmacokinetics of TMZ is unknown, and a pilot study was performed to assess the pharmacokinetics of TMZ given via various routes to 29 patients (27 malignant melanomas, 2 gliomas) with or without sequential administration of i.v. fotemustine.

METHODS: On day 1, TMZ was given intravenously (i.v.), orally (p.o.), or by intra-hepatic arterial infusion (h.i.a.) at four ascending dose levels (150 to 350 mg/m² per day). On day 2 the same dose of TMZ was given by the same route (or by another route in six patients for determination of its bioavailability), followed 4 h later by fotemustine infusion at 100 mg/m². Plasma and urinary levels of TMZ were determined on days 1 and 2 by high-performance liquid chromatography after solid-phase extraction.

RESULTS: The pharmacokinetics of i.v. TMZ appeared linear, with the area under the curve (AUC) increasing in proportion to the dose expressed in milligrams per square meter ($r = 0.86$ and 0.91 for days 1 and 2, respectively). The clearance after i.v. administration was 220 ± 48 and 241 ± 39 ml/min on days 1 and 2, respectively. The apparent clearance after p.o. and h.i.a. administration was 290 ± 86 and 344 ± 77 ml/min, respectively. The volume of distribution of TMZ after i.v., p.o., and h.i.a. administration was 0.4, 0.6, and 0.6 l/kg on day 1 and 0.5, 0.5, and 0.6 l/kg on day 2, respectively. The absolute bioavailability of TMZ was 0.96 ± 0.1 , regardless of the sequence of the i.v.-p.o. or p.o.-i.v. administration, confirming that TMZ is not subject to a marked first-pass effect. A comparison of TMZ pharmacokinetics after i.v. and h.i.a. treatment at the same infusion rate revealed little evidence of hepatic extraction of TMZ. However, the systemic exposure to TMZ (AUC) appeared to decrease at a lower infusion rate. TMZ excreted unchanged in the urine accounted for $5.9 \pm 3.4\%$ of the dose, with low within-patient and high interpatient variability. TMZ crosses the blood-brain barrier and the concentration detected in CSF amounted to 9%, 28%, and 29% of the corresponding plasma levels (three patients). The equilibrium between plasma and ascitic fluid was reached after 2 h (assessed in one patient).

CONCLUSION: The sequential administration of fotemustine at 4 h after TMZ treatment had no clinically relevant influence on the pharmacokinetics of TMZ. The potential clinical effect of TMZ given by h.i.a. or by locoregional administration has yet to be established, as has the impact of the infusion duration on patients' tolerance and response rate.

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