

PubMed

Display Settings: Abstract[Ann Oncol.](#) 1999 Jul;10(7):831-8.

Sequential administration of temozolomide and fotemustine: depletion of O6-alkyl guanine-DNA transferase in blood lymphocytes and in tumours.

Gander M, Leyvraz S, Decosterd L, Bonfanti M, Marzolini C, Shen F, Liénard D, Perey L, Colella G, Biollaz J, Lejeune F, Yarosh D, Belanich M, D'Incalci M.

Centre Pluridisciplinaire d'Oncologie, Lausanne, Switzerland.

Abstract

BACKGROUND: The DNA repair protein O6-alkylguanine-DNA alkyl transferase (AT) mediates resistance to chloroethylnitrosoureas. Agents depleting AT such as DTIC and its new analogue temozolomide (TMZ) can reverse resistance to chloroethylnitrosoureas. We report the results of a dose finding study of TMZ in association with fotemustine.

PATIENTS AND METHODS: Twenty-four patients with metastatic melanoma or recurrent glioma were treated with escalating dose of oral or intravenous TMZ ranging from 300 to 700 mg/m², divided over two days. Fotemustine 100 mg/m² was given intravenously on day 2, 4 hours after TMZ. AT depletion was measured in peripheral blood mononuclear cells (PBMCs) and in selected cases in melanoma metastases and was compared to TMZ pharmacokinetics.

RESULTS: The maximum tolerated dose (MTD) of TMZ was 400 mg/m² (200 mg/m²/d) when associated with fotemustine the 2nd day with myelosuppression as dose limiting toxicity. The decrease of AT level in PBMCs was progressive and reached 34% of pretreatment values on day 2. There was however wide interindividual variability. AT reduction was neither dose nor route dependent and did not appear to be related to TMZ systemic exposure (AUC). In the same patients, AT depletion in tumour did not correlate with the decrease of AT observed in PBMCs.

CONCLUSIONS: PBMCs may not be used as a surrogate of tumour for AT depletion. Further study should concentrate on the pharmacokinetic pharmacodynamic relationship in tumour to provide the basis for individually tailored therapy.

PMID: 10470431 [PubMed - indexed for MEDLINE] [Free full text](#)

[+](#) [Publication Types, MeSH Terms, Substances](#)

[+](#) [LinkOut - more resources](#)