Alkylating antineoplastic agent

An alkylating antineoplastic agent is an alkylating agent used in cancer treatment that attaches an alkyl group (CnH2n+1) to DNA.

The alkyl group is attached to the guanine base of DNA, at the number 7 nitrogen atom of the purine ring.

Since cancer cells, in general, proliferate faster and with less error-correcting than healthy cells, cancer cells are more sensitive to DNA damage—such as being alkylated. Alkylating agents are used to treat several cancers. However, they are also toxic to normal cells (cytotoxic), particularly cells that divide frequently, such as those in the gastrointestinal tract, bone marrow, testicles and ovaries, which can cause loss of fertility. Most of the alkylating agents are also carcinogenic. Hyperthermia therapy is especially effective at enhancing the effects of alkylating agents.

Glioma treatment resistance to alkylating chemotherapy is mediated via O6-methylguanine-DNA methyltransferase (MGMT).

Lipp et al. hypothesized that a CD45/HAM56/MGMT double-stained cocktail would improve MGMT discrimination in tumor cells versus inflammatory cell and endothelial cells (IEC). Total MGMT protein was quantified by IHC on 982 glioblastomas (Glioblastoma) and 199 anaplastic astrocytomas. Correcting for IEC was done by a CD45/HAM56/MGMT 2-color cocktail. Lowest IEC infiltrates (IEC “cold spots”) were identified to quantitate MGMT as well as the percentage of IEC% in the IEC cold spots. MGMT promoter methylation (PM) was also determined. Among the Glioblastoma biopsies, mean uncorrected and corrected MGMT% were 19.87 (range 0-90) and 16.67; mean IEC% was 18.65 (range 1-80). Four hundred and fifty one (45.9%) Glioblastoma biopsies were positive MGMT PM. Both uncorrected and corrected MGMT% positivity correlated with PM. All 3 MGMT scores correlated with overall survival (OS) in Glioblastoma's. Cold spot IEC% was also positively associated with OS. These effects remained in a multivariate model after adjusting for age and disease status. Prognosis determined by correcting MGMT% score for IEC% is not improved in this analysis. However, IEC COLD SPOT score does provide additional prognostic information that can be gained from this correction method [1)].

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Lipp ES, Healy P, Austin A, Clark A, Dalton T, Perkinson K, Herndon JE, Friedman HS, Friedman AH, Bigner DD, McLendon RE. MGMT: Immunohistochemical Detection in High-Grade Astrocytomas. J Neuropathol Exp Neurol. 2018 Nov 30. doi: 10.1093/jnen/nly110. [Epub ahead of print] PubMed PMID: 30500933.