A Probable Mechanism for Hyperpigmentation by Fotemustine

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We were most interested in the case report by Claudy et al. [1]. Recently, we used ¹⁴C-chloroethyl-labelled fotemustine and established that it is a potent inhibitor of thioredoxin reductase in the human epidermis and in human metastatic melanoma [2, 3]. The drug inactivates thioredoxin reductase by alkylation of its thiolate-active site with a 'C-chloroethyl group. Thioredoxin reductase has been shown to be very important in the regulation of melanin biosynthesis by reduction of its natural, substrate thioredoxin. Reduced thioredoxin is an allosteric inhibitor of human tyrosinase, the key enzyme in melanin biosynthesis, and down-regulates enzyme activity to 30% of normal levels [4-6]. Tyrosinase expression is the same in the human epidermis regardless of skin type; with this enzyme being subject to down-regulation in fair-skinned individuals [7].

We treated 53 patients with metastatic melanoma intravenously with fotemustine monotherapy and 7 patients with 36 subcutaneous and cutaneous melanoma metastases by local injections of high concentrations (55×10^{-3} M) of the drug, subcutaneously and intratumorally, in a sequence of 20 min over 2 h [8-10]. So far, we have not observed the described supravenuous hyperpigmentation in any of our cases.

We would like to suggest the following hypothesis for the observed hyperpigmentation in these 2 patients. Fotemustine diffuses rapidly through membranes, and therefore during a longer infusion time, a higher concentration of the drug would be delivered at the point of entry (i.e. the arm). If the venous blood of these 2 patients was more deoxygenated, e.g. due to chronic obstructive pulmonary disease or heavy smoking, then a more reduced local environment would cause a 'rapid reaction of fotemustine with target thioproteins such as thioredoxin reductase [3]. As a consequence, depletion of the reduced thioredoxin pool would activate tyrosinase resulting in the observed hyperpigmentation [5, 6].

References

Claudy AL, Lévine V, Boucheron S: Serpentine supravenuous hyperpigmentation induced by the nitrosourea fotemustine. *Dermatology* 1992;185:70-72.

Schallreuter KU, Gleason FK, Wood JM: The mechanism of action of the nitrosourea anti-tumor drugs on thioredoxin reductase, glutathione reductase and ribonucleotide reductase. *Biochim Biophys Acta* 1990;1054:14-20. Schallreuter KU, Wood JM: Sensitivity and resistance to human metastatic melanoma to the new chloroethylnitrosourea anti-tumor drug fotemustine. *Biochim Biophys Acta* 1991;1096:277-283.

Schallreuter KU, Wood JM: The role of thioredoxin reductase in the reduction of free radicals at the surface of the epidermis. *Biochim Biophys Res Commun* 1986;136:630-637. Wood JM, Schallreuter KU: Reduced thioredoxin inhibits melanin biosynthesis: Evidence for the formation of a stable bis cysteinyl complex with tyrosinase. *Inorganica Chimica Acta* 1988;151-157. Wood JM, Schallreuter KU: Studies on the reactions between human tyrosinase, superoxide anion, hydrogen peroxide and thiols. *Biochim Biophys Acta* 1991;1074:378-385. Iwata M, Corn I, Iwata S, Everett MA, Fuller BB: The relationship between tyrosinase activity and skin color in human foreskins. *J Invest Dermatol* 1990;95:9-15.

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Schallreuter KU, Wood JM, Mensing H, Breitbart EW: Local treatment of cutaneous and subcutaneous metastatic malignant melanoma with fotemustine. *Cancer Chemother Pharmacol* 1991;29:167-171.

Schallreuter KU, Wenzel E, Brassow FW, Berger J, Breitbart EW, Teichmann W: Positive phase II study in the treatment of advanced malignant melanoma with fotemustine. *Cancer Chemother Pharmacol* 1991;29:85-87. Mohr P, Weichenthal M, Altenhoff J, Schallreuter KU, Ring J, Breitbart EW: Systemic chemotherapy with fotemustine in stage IV malignant melanoma (abstract). *Arch Dermatol Res* 1992;248:19.

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