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# The effect of bioreduction on the oncogenicity of nitroimidazoles*

Much of Sessions C and D was dominated by a discussion on a group of nitroheterocyclic compounds which show great promise as radio- and chemosensitizers for the treatment of cancer. One mechanism by which they produce a selective effect on tumor cells, as opposed to normal tissues, stems from their bioreduction under conditions of hypoxia.

To round out this program and to present a balanced picture, it should be pointed out that these agents, which show such promise for the treatment of cancer, may on the basis of *in vitro* oncogenic transformation assays [1–3] be capable of inducing cancer. All of the published results from our laboratory to date relate to drug treatments under aerated conditions, where metabolism and bioreduction are of little importance. Under these conditions, the more recently developed compounds show a great variability in oncogenic potential [2].

Compared with the lead compound, Misonidazole, SR-2508, the radiosensitizer favored for future Phase III clinical studies in the United States, produces about five times more transformants than MISO for the same drug concentration and equal sensitizing effectiveness [3]. This is probably a consequence of the amide in the side-chain. The compound chosen for clinical trials in the U.K., Ro-03-8799, is about equal to MISO in transforming potential [2]; the apparent slight increase in effectiveness can probably be accounted for by an increased concentration of the drug within cells compared with the supernatant. This has been attributed to the pH dependence of the lipophilicity of the drug [4].

A most interesting group of compounds are the dual function sensitizers which are made up of a conventional electron affinic nitroimidazole group, together with an aziridine ring on the side-chain which acts as a monofunctional alkylating agent. The lead compound, RSU-1069, is a potent radiosensitizer, but is also highly cytotoxic as well as being an efficient inducer of transformed foci [2, 5]. It remains to be seen whether substitutions on the aziridine ring can preserve the remarkable sensitizing properties, while reducing the toxicity and transforming potential.

We have recently started transformation experiments under hypoxic conditions. Technical difficulties have previously made such experiments impractical. Figure 1 shows preliminary data from an experiment which compares directly MISO and SR-2508 under aerated and hypoxic conditions. There are 3 points to be made.

i. The much greater effectiveness of SR-2508 in producing transformants under aerated conditions is again evident from this experiment.
ii. Many more transformants are produced under hypoxic than aerated conditions, presumably because of the bioreduction of the drug under these conditions.
iii. The big difference in oncogenicity between MISO and SR-2508, so evident under aerated conditions, is absent under hypoxic conditions. This finding would seem to imply that slight differences in composition of the side-chain is dwarfed into insignificance once metabolism and bioreduction are involved, since the products of bioreduction are so much more effective at producing transformants.

In summary, the nitroimidazoles are clearly seen to be potentially carcinogenic. There is a substantial variation in the transformation incidence produced by various compounds used or proposed for clinical use. A substantial increase in oncogenicity is apparent under hypoxic conditions where bioreduction occurs, and in these circumstances the variability in oncogenicity between different compounds, commonly found under aerated conditions, is less marked. However, in all cases the nitroimidazole sensitizers are far less potent than the commonly used chemotherapy agents such as *Cis*-platinum [1]. As a very rough estimate, the widespread use of hypoxic cell sensitizers, such as Misonidazole, ought to be expected to result in an incidence of second malignancies in long-term survivors of about 1%. This would be a small price to pay if radiosensitizers lead to a significant increase in tumor control and patient survival.

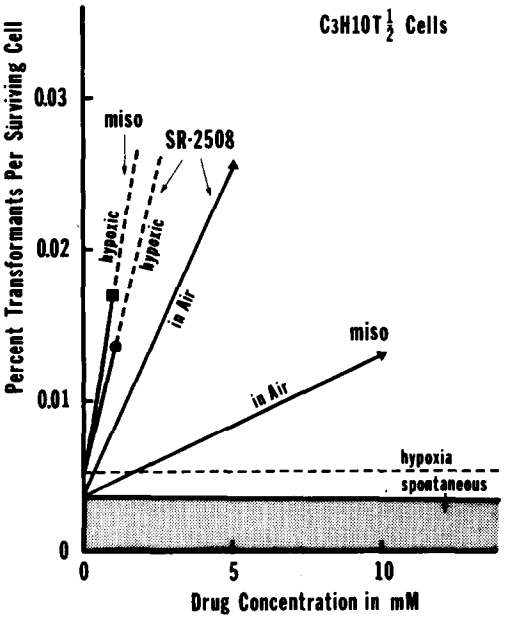


Fig. 1. Preliminary data for transformation frequency per surviving cell as a function of drug concentration. Under aerated conditions, SR-2508 produces about 5 times as many transformants as MISO at a given concentration—presumably because of the amide group in the side-chain. Under hypoxic conditions, transformation frequency is greatly increased compared with aerated conditions. In addition, the large differential in oncogenicity between Misonidazole and SR-2508 has disappeared. The presumed explanation is that the products of bioreduction are far more effective at producing transformation and dwarf the difference in the side-chains.

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