Letters to the Editor

Cytochrome P450 enzymes and tumor therapy

To the Editors: McFadyen et al. (1) have contributed a review on the aspects of cytochrome P450–related tumor therapy that is worth reading. It clearly shows the potential of such an approach for cancer therapy. Based on my own experience, I would kindly like to point out a few additional issues that may add to the excellent review. Ifosfamide and cyclophosphamide both use some more cytochrome P450 subenzymes (e.g., CYP2B1 and CYP3A4; refs. 2, 3). The problem for using both substances in solid tumors, namely in the elderly, arises from severe side effects that prevent their further clinical use despite promising response rates (e.g., in pancreatic cancer; refs. 4, 5). One approach therefore was to use the significant antitumoral potential but to spare the patient from the side effects. This can be achieved by establishing a second site of enzyme conversion at or in the tumor by either transfecting tumor cells in an experimental setting with a converting enzyme (6) or bringing cells transfected with one of the metabolizing enzymes close to the tumor (7). We have chosen the latter approach, demonstrating complete responses in the animal model and stable disease as well as some partial responses in a clinical phase I study in advanced pancreatic cancer (8). There were no side effects from the chemotherapy in these patients. As a strategy to “maximize efficacy and minimize toxicity,” as claimed by McFadyen et al., we have microencapsulated the genetically engineered cells to create “magic bullets” (9). This concept, although working, can be improved in several ways. One of them is to add the cytochrome reductase to the system as described by Jounaidi and Waxman (10). Another one would be the addition of less toxic antitumoral drugs metabolized by the P450 system such as AQ4N (11). This kind of “gene therapy” (gene-directed enzyme prodrug therapy) may not be very sophisticated but has the charm of simplicity and has shown proof of concept.

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References

In Response: We are delighted that Dr. Lohr has enjoyed our review (1) and is happy to reiterate our comments on the use and importance of bioreductive drugs, such as AQ4N, as novel targets for gene-directed enzyme prodrug therapy (2). As Dr. Lohr appreciates, one of the concerns in the delivery of gene-directed enzyme prodrug therapy is in maximizing the efficacy of the converting enzyme (in this case, CYP2B1), and we thank him for highlighting the article by Jounaidi and Waxman, describing the addition of cytochrome P450 reductase to the system (3). As highlighted in the review, the specific localization of individual P450s in tumor cells, particularly CYP1B1 (4), is now being exploited by a range of novel therapies (1). The most advanced of these is an immune-based therapy targeting the specific expression of CYP1B1 in tumor cells (5). Preclinical trials of a CYP1B1 DNA vaccine Zyc300 have been shown to induce a specific T-cell response to destroy cancer cells (1, 5). A recent phase I/II study, with Zyc300 in late-stage metastatic cancer patients, reported that the CYP1B1 vaccine was well tolerated. Indeed, “80% of patients receiving the maximum number of doses showed a biological response to the vaccine.”1 In addition, “a number of the patients have had unexpected clinical responses to subsequent salvage therapy including two with complete responses and two with partial responses.”1 The potential to tailor patient-specific therapeutic regimens (including

gene-directed enzyme prodrug therapy, prodrugs, clinical inhibitors, and immunotherapy) against individual \( \text{P}450 \)s within tumor cells to improve the treatment of a variety of human tumors is getting ever closer.

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References


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