Why Some Tumors Fail to Respond to Chemotherapy

Comments on a New Model of Drug Sensitivity and Resistance

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Drug resistance is the major cause of failure of chemotherapy for malignant tumors. In an excellent paper in this issue of *Acta Oncologica*, Pusztai and colleagues from the University of Texas MD Anderson Cancer Center propose an interesting model of drug resistance in ovarian cancer, which should have implications also for other solid tumors (1). Their hypothesis is based on previous models by Skipper, Goldie–Coldman and Norton–Simon, and has been further developed to account for several clinical observations in ovarian cancer chemotherapy, such as the limited benefits of adjuvant chemotherapy and the lack of efficacy of high-dose chemotherapy in primary drug resistance. The authors make a convincing case for their new model by combining such clinical observations with results of investigations of cellular mechanisms of drug resistance in ovarian carcinoma.

The model is based on the well-documented phenomenon of clonal progression in tumors, and describes changes in drug sensitivity during different stages of clonal evolution of the neoplastic cells. The authors start from the fundamental, but sometimes overlooked, fact that many tumors are more drug sensitive than the corresponding normal tissue. During the early development of a malignancy, the tumor cells may retain the 'physiologic resistance' of the normal tissue of origin and be unresponsive to chemotherapy. As the authors point out, alternative treatments other than cytotoxic chemotherapy may be of benefit in such tumors.

At some later stage of tumor evolution, malignant cell clones may lose the mechanisms that protect the normal tissue, and thus become drug-sensitive. As Pusztai et al. (1) point out, the mechanisms of increased drug sensitivity in tumor cells are not well characterized at present, but their model is supported by recent findings that alterations in tumor suppressor- and oncogene activity may lead to drug sensitivity, as well as investigations showing loss of expression of genes involved in apoptosis and drug exclusion in ovarian cancers. The authors indicate that this hypothesis helps to explain the clinical observation that tumors that have recurred after initial chemotherapy may respond to re-treatment with the same drug(s), since initially 'physiologically resistant' tumor cells may over time develop drug sensitivity.

With further tumor progression some neoplastic cell clones may acquire 'pathologic drug resistance'. This phenomenon has been much more extensively studied, and several mechanisms of resistance have been identified, involving alterations in drug uptake and exclusion, drug inactivation, alterations in target proteins, DNA damage repair and regulation of apoptosis (2). However, much work is still needed to define the importance of several of these mechanisms for clinical drug resistance.

The discussion of the role of DNA repair for drug resistance by Pusztai et al. (1) requires some clarification. As the authors point out, increased DNA nucleotide excision repair may contribute to tumor resistance to DNA-damaging drugs, such as alkylating and platinating agents. In contrast, alterations in mismatch repair may play an opposite role. DNA lesions induced by several classes of chemotherapeutic drugs, including methylating and platinating agents and topoisomerase II inhibitors, are recognized by the DNA mismatch repair machinery. Unsuccessful processing of such lesions by the mismatch repair system may lead to persistent DNA damage which, in turn, activates signal transduction pathways leading to apoptosis. In contrast, in mismatch repair-deficient cells the damage is unrecognized, resulting in drug resistance (3, 4).

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Evolution of 'pathologic drug resistance' may lead to high levels of resistance, which may not be possible to overcome by the limited increases in drug dose obtained by the current technology of high-dose chemotherapy. This is likely to explain the poor results obtained with high-dose therapy in tumors resistant to conventional chemotherapy. Furthermore, what is implicit in the model of clonal progression is the prediction that several clones with different mechanisms of drug resistance may evolve in a tumor. This is in accordance with the limited success so far obtained with attempts at modulation of single-drug resistance factors, such as pharmacological reversal of p-glycoprotein-mediated multi-drug resistance (2). The conclusion to be drawn from this is that assays of several putative drug resistance factors are required to characterize advanced tumors, and that sucessful chemotherapy may have to involve reversal of multiple resistance mechansisms.

Pusztai and colleagues base their model of drug resistance on genetic changes in the tumor cell population occurring during tumor progression. However, reality is, as usual, probably even more complex. The interaction of the neoplastic cells with normal cells in the surrounding tissue may alter the gene expression pattern, and thus the phenotype, of the tumor. For instance, Fidler and colleagues (also at MD Anderson) have shown in elegant experiments that the organ environment can reversibly induce the p-glycoprotein-mediated multidrug-resistant phenotype in tumor cells (5). Thus, murine colon cancer cells were doxorubicin-sensitive when growing subcutaneously, but growth as metastases in the lung induced expression of mdr-1, resulting in doxorubicin resistance. When removed from the lung environment, the cells again reverted to the sensitive phenotype. This type of interaction between neoplastic cells and surrounding tissue, resulting in epigenetic changes in the tumor, may be important and may at least in part explain why metastases in different organ environments respond differently to chemotherapy.

The new model of drug resistance presented by Pusztai and colleagues should have implications not only for ovarian cancer but also for other solid tumors. This model will be valuable as a tool to consider the problem of drug resistance more systematically, and to help us identify improved strategies of chemotherapy.

In particular, the phenomenon of drug sensitivity following loss of resistance mechanisms in tumors should be kept in mind. There may thus be a critical window of opportunity when the tumor consists mainly of cell populations that have lost the 'physiologic' drug resistance and not yet acquired 'pathologic' forms of resistance. If patients with such tumors can be identified, they are the ones who are likely to benefit from intense chemotherapy with a curative intent. To be able to select the appropriate chemotherapy, better knowledge of mechanisms of 'physiologic resistance' to individual drug classes is essential, which may enable us to predict which type(s) of drug a particular tumor may be sensitive to. So far, most investigations of drug sensitivity and resistance have focused on mechanisms of resistance in advanced tumors, corresponding to 'pathologic drug resistance', according to the present model. Henceforth, studies to identify markers of loss of normal drug defense mechanisms in tumors should also have high priority, since they may lead to improvement in the methods used to select patients who may be cured by the appropriate chemotherapy.

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