P-GLYCOPEPTIDASE - A MARKER OF CANCER-CELL BEHAVIOR

Resistance to a broad array of cytotoxic drugs - multidrug resistance - is thought to be a major reason chemotherapy fails to cure most cancers. Multidrug resistance has been studied intensively since the human MDR1 gene was identified almost 10 years ago. Increased levels of the MDR1 product, called P-glycoprotein, are often associated in vitro with reduced intracellular concentrations of several anticancer drugs derived from plants, such as anthracyclines (e.g., doxorubicin), epipodophyllotoxins (e.g., etoposide), vinca alkaloids (e.g., vincristine), daunomycin, and paclitaxel. When cells are grown in increasing concentrations of one of these cytotoxic drugs, populations of cells that overexpress the MDR1 gene may be selected. These cells, selected by only one drug, have cross-resistance to all the above-mentioned drugs.

P-glycoprotein is a transmembrane glycoprotein that is normally present in cells of the adrenal cortex, biliary canaliculi, endothelium of the blood-brain and blood-testicle barriers, placenta, gastrointestinal epithelium, proximal renal tubuli, and some bone marrow stem cells. In many of these organs, P-glycoprotein is thought to act as a detoxifying agent by pumping toxins or xenobiotics (including anticancer drugs) out of cells. In other organs, such as the adrenal gland and the gravid uterus, it may transport steroid hormones. P-glycoprotein belongs to a large superfamily of highly conserved ATP-binding cassette transport proteins, and its amino acid sequence resembles those of many bacterial and eukaryotic transport proteins.

Increased levels of P-glycoprotein are common in cancer cells. Moreover, levels of the glycoprotein can increase after chemotherapy, when the tumor becomes refractory to treatment. The presence of increased levels of P-glycoprotein in several types of tumor has been correlated with poor responses to chemotherapy and short progression-free survival and overall survival.

In this issue of the Journal, Baldini et al. report a strong correlation between the presence of increased levels of P-glycoprotein and the prognosis in patients with osteosarcoma. Osteosarcoma is a rare and extremely aggressive cancer that most commonly affects adolescents. Preoperative and adjuvant chemotherapy has dramatically improved the prognosis of patients with nonmetastatic osteosarcoma. Nevertheless, about 50 percent of patients who undergo radical surgical resection and receive aggressive combination chemotherapy relapse. Salvage therapy (chemotherapy with or without surgery) benefits only a minority of these patients. So far, the most important predictor of disease-free survival and overall survival is the histologic response to preoperative chemotherapy - that is, the amount of chemotherapy-induced necrosis in the tumor.

Baldini et al. found that the P-glycoprotein status of the primary biopsy specimen was a better prognostic marker than tumor necrosis. Patients with tumors that had high levels of P-glycoprotein, as assessed immunohistochemically, had twice the relapse rate of patients with P-glycoprotein-negative tumors. This difference was independent of the amount of tumor necrosis found in the surgical specimen after preoperative chemotherapy.

These findings suggest that P-glycoprotein status might be used to identify patients with osteosarcoma who are at higher-than-usual risk of metastases and thereby serve as a marker to select patients for aggressive therapy, such as high-dose chemotherapy with transplantation of peripheral stem cells. The authors suggest that the use of drugs, such as cyclosporine, that can impair the pumping function of P-glycoprotein and thus reverse multidrug resistance may be effective in patients who have relapsed or may prevent multidrug resistance in previously untreated patients whose tumors have increased levels of P-glycoprotein.

It is interesting that Baldini et al. did not observe any correlation between P-glycoprotein status and the extent of tumor necrosis. In other words, the expression of P-glycoprotein was unrelated to the response of tumor cells to chemotherapy. In fact, these two phenomena remained independent variables in a multivariate analysis. This suggests that, at least in patients with osteosarcoma, the presence of P-glycoprotein may be not simply a marker of tumor chemosensitivity but also a sign of tumor aggressiveness. Similar observations have been made in colon cancer, in which 50 percent of the invading carcinoma cells at the leading edge of the tumor expressed P-glycoprotein. The expression of P-glycoprotein by these carcinoma cells was strongly correlated with a greater-than-usual incidence of vessel invasion and lymph-node metastases. Moreover, in half the patients with P-glycoprotein-negative tumors, the lymph nodes expressed P-glycoprotein. Another relevant finding is that P-glycoprotein is more frequently expressed in locally advanced breast cancers, which are often very aggressive, than in smaller, more indolent tu-
One could hypothesize that cancer cells use P-glycoprotein to pump out the cytokines that mediate the process of invasion and metastasis.

In the study by Baldini et al., as in several others like it, it is difficult to conclude that the ability of P-glycoprotein to extrude drugs from the tumor cells was clinically important. The chemotherapy given to the patients included methotrexate, cisplatin, and ifosfamide, which are not substrates of P-glycoprotein. In another study of the problem, the expression of a different molecule related to drug resistance, lung resistance protein, which is not on the cell surface but in the cytoplasm, correlated with the prognosis of patients with ovarian cancer who were being treated with cisplatin. It would therefore be interesting to see whether the presence of lung resistance protein is a marker of resistance in osteosarcoma, in which cisplatin also has a major therapeutic role.

Several drugs, such as calcium-channel blockers and cyclosporine, can efficiently reverse the multidrug-resistance phenotype in vitro. These compounds act mainly through inhibition of the drug pump by P-glycoprotein. As a result, they enhance the intracellular concentration of cytotoxic drugs (Fig. 1). Clinical studies of such agents given in combination with chemotherapy have been performed in patients with hematologic cancers or solid tumors. Many of these studies attempted to achieve plasma concentrations of these agents that matched the concentrations that were effective in vitro. However, the importance of the plasma concentration is unclear, because we have virtually no knowledge of the concentrations of these agents and cytotoxic drugs in tumors. Moreover, many reversing agents have been toxic at doses that mimic the conditions in vitro; consequently, a number of studies actually used suboptimal concentrations.

Cortisol and probably several other endogenously produced substances are also extruded by P-glycoprotein. These endogenous products may compete with exogenous drugs for the P-glycoprotein pump. It is thus not surprising that agents that reverse the multidrug-resistance phenotype are of limited benefit.

Despite occasional responses in patients with hematologic cancers, in which tumor cells are more directly exposed to a drug than are the cells in solid tumors, and despite the positive results of a small, randomized study of the addition of verapamil to chemotherapy in untreated non–small-cell lung cancer, three recent large, randomized trials failed to show any benefit of agents that reverse the multidrug-resistance phenotype in terms of the response to chemotherapy or the length of survival. The addition of verapamil to a regimen consisting of vincristine, doxorubicin, and dexamethasone had no effect in patients with refractory multiple myeloma. Two other large, randomized studies of untreated patients with small-cell lung cancer and breast cancer also failed to demonstrate any benefit of adding verapamil or quinidine to chemotherapy. Drug resistance is very likely multifactorial. For example, cells with defective transport of antineoplastic drugs have been shown to have increased levels of yet another ATP-binding cassette transport protein, called MRP (multidrug-resistance–associated protein).

Some agents that reverse the multidrug-resistance phenotype, such as verapamil and cyclosporine, influence the pharmacokinetics of anticancer drugs, possibly by decreasing their elimination and increasing their plasma concentrations by 40 to 60 percent, thereby increasing their toxicity. Apart from the adequacy of plasma concentrations of the reversing agents, other factors must be considered when one is designing clinical studies of the treatment of osteosarcoma. The role of these agents can be assessed only by a randomized study in which the target plasma concentration of the anticancer drug over time is matched in the group given the reversing
agent and the group not given the agent. The steep dose--response relation of several anticancer drugs is well known. Moreover, the plasma concentration of doxorubicin, the chief metabolite of doxorubicin, increases more than threefold when doxorubicin is given together with cyclosporine. Because doxorubicin is a less potent anticancer drug and may be more cardiotoxic than its parent, proposed studies of agents that may reverse the multidrug-resistance phenotype are not without risk.

Given the disappointing results of clinical trials of agents that reverse the multidrug-resistance phenotype and the uncertain role of P-glycoprotein expression in inducing drug resistance in human cancers, other approaches, such as high-dose myeloablative chemotherapy followed by the trans fusion of peripheral stem cells, may have higher priority in patients whose tumors have high levels of P-glycoprotein.

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REFERENCES


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THE COMPUTER-BASED PATIENT RECORD AND CONFIDENTIALITY

In various ways computers can help people become more active participants in their own health care and that of family members, as emphasized earlier by Kassirer. Computers can help people acquire medical information, interact with care givers, connect with support groups when illness strikes, and in some cases, carry out a treatment plan. Electronic linkage of patients and their families to support groups and medical libraries is well under way and is likely to increase in popularity as computers become standard equipment in the American home. Information bestows power, and making medical information more easily accessible is a way of empowering patients. In theory at least, the better-informed patient will be in a better position to consider various options in addressing a medical problem and to evaluate medical advice.

Most advocates of the use of the computer in medical care have different aims. They are more interested in the benefits of computer-based medicine to the health care industry and, not incidentally, to the computer industry. In 1991 the Institute of Medicine (IOM) released an influential report, The Computer-Based Patient Record: An Essential Technology for Health Care. It advocated the adoption of the computer-based patient record as standard medical practice in the United States. As the report said, "CPRs [computer-based patient records] and CPR systems can respond to health care's need for a 'central nervous system' to manage the complexities of modern medicine — from patient care to public health to health care policy." The report described the computer-based patient record as a continuous chronologic history of a patient's medical care linked to various aids for users, such as reminders and alerts to clinicians, and clinical decision-making systems.

The IOM report led to the creation of the Computer-Based Patient Record Institute, an advocacy group that is supported by corporations in the health care, insurance, data-processing, and computer industries, as well as by some professional groups. Last year's proposals for health care reform and some bills currently before Congress include provisions for the establishment of a National Health Care Data Network. Such a network would contain records on every medical encounter in the United States. These measures at the federal level reflect the effectiveness of efforts to promote the computer-based patient record.

In spite of the computer's obvious usefulness, its use in medical care is replete with problems. The greatest concern is the threat to confidentiality. Even before the introduction of the computer, confidentiality deteriorated as care provided by large groups became more