Are Immunosuppressive Anticancer Drugs Self-defeating?1

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A substantial body of evidence indicates that tumors of experimental animals, whether elicited by carcinogens or viruses, possess neoantigens capable of provoking typical immune responses. In many instances it appears that these neoplasms gain a foothold and finally prove lethal because they escape detection or destruction by immune mechanisms. Whenever the acquisition of immunity against tumor antigens fails—because of either immunologic tolerance (29) or defective immunologic surveillance (7)—neoplastic growth is favored. It may be more than coincidence that carcinogens are among the most powerful immunosuppressive agents known (30), that oncogenic viruses depress immune responses (32), and that the immunosuppressive drug 6-mercaptopurine (6-MP) is carcinogenic (9). In light of this, it seems paradoxical to treat cancer with drugs that profoundly inhibit the very system considered essential for protection against neoplastic cells. If an antitumor drug can retard the rejection of a kidney allograft, why not the same effect with regard to an antigenic neoplasm? It is, after all, only an accident of priorities that many drugs are known as anticancer agents rather than immunosuppressants.

It is reasonable to inquire whether or not observations on tumor immunity made in mice and chickens have any relevance to human neoplasms. All that can be said at present is that the data are inadequate. There is, however, an important clue revealed by certain types of immunologic deficiencies. In these diseases there is an abnormally high incidence of leukemia and lymphoma (12), which is at least consistent with the notion that the growth of some neoplasms is favored by defective immunity. A clearcut demonstration of neoantigens in human neoplasms could provide a means to test the hypothesis that immunosuppressive anticancer drugs, by impairing the patient's immunity, might be self-defeating.

Six types of chemicals—alkylating agents, purine analogs, folic acid antagonists, halogenated pyrimidines, the vinca alkaloids, and the corticosteroids—are the stock in trade of cancer chemotherapists. Each of them very significantly depresses the immune system (10, 36). Each can completely inhibit the synthesis of circulating antibodies, especially when given close to the time of immunization. When only moderate doses of cyclophosphamide (33), 6-MP (31), or Methotrexate (MTX) (5) are given, antibodies are formed, but they are almost entirely of the IgM class. Thus, these drugs appear to inhibit IgG antibody synthesis in a selective manner. Presumably immunity can also be impaired, but, in general, large doses of drugs are required. In addition to effects on circulating antibody formation, these agents depress cellular-immune (delayed hypersensitivity) responses. In the case of 6-MP this type of immunity is more readily inhibited than IgG production (6). The retention of allografts can be greatly prolonged by cyclophosphamide, 6-MP, and MTX and, when antigenic differences between donor and host are not strong, an even greater effect is seen (37).

An intriguing property of the immunosuppressive anticancer drugs is their capacity to condition an adult animal for the acquisition of specific immunologic tolerance. Tolerance of a variety of antigens, including polyepptides (38), proteins (35), viruses (13), erythrocytes (2), and allografts (14), has been acquired by animals [and probably humans (22)] treated with cyclophosphamide, 6-MP, or MTX. The tolerance is specific for the antigen administered during the period of chemotherapy and closely resembles the form of immunologic tolerance acquired by neonates. Prior sensitization does not preclude the induction of tolerance of the sensitizing antigen by chemotherapy (21). Of singular importance is the observation—made repeatedly—that only a relatively brief course of drug treatment is required to condition an animal for the induction of immunologic tolerance.

There is every indication that the representative anticancer drugs mentioned before are immunosuppressive in man, although the evidence concerning corticosteroids is not entirely convincing. Studies carried out with cyclophosphamide, 6-MP, 6-thioguanine, azathioprine, MTX, or 5-fluoro-2'-deoxyuridine (FUDR) in either normal humans (23), patients with immunologic diseases (40), or cancer patients (16) demonstrated impaired responses to a variety of antigens, with primary and secondary immune responses, delayed hypersensitivity, and skin allograft rejection being affected to one degree or another. The doses of drugs used in these experiments were those generally employed in the treatment of neoplasms. As a rule, the weaker the antigenic stimulus, the greater was the immunosuppressive effect of the drug under study. In instances when short-term (five days) chemotherapy was employed, suppression of antibody synthesis lasted at least four weeks, at which time the experiment was terminated (15). Preexisting antibodies have been resistant to depression, except when high doses of antimetabolites were given (26).

A notable effect of the immunosuppressive drugs is inhibition of transplantation immunity. Indeed, the current practice of transplantation surgery depends in large measure on the immunosuppressive properties of the purine analogs, such as 6-MP and azathioprine. Not only can immune responses to

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normal tissues be inhibited, but those to grafts of neoplasms can also be profoundly depressed. The pioneering work of Toolan (41, 42) demonstrated that cortisone treatment can significantly prolong the survival of malignant xenografts and allow the serial propagation of human tumors in cortisone-treated hamsters, rats, and mice. Cortisone has similar effects when allogeneic neoplasms (34) are used and, in some situations, also appears to promote widespread metastases (1).

An illuminating series of experiments has been carried out utilizing a transplantable leukemia, L1210, and its antifolic-resistant variants. These neoplasms are rejected by allogeneic recipients in a manner typical of allografts. However, treatment of recipients of an antifolic-resistant leukemia with MTX resulted in progressive tumor growth and death (18). It was shown that inocula containing only very small numbers of allogeneic tumor cells could evolve into lethal neoplasms in MTX-treated mice (19). It may be of some interest that the degree of immune suppression necessary to permit the unrestricted growth of this allogeneic neoplasm could be brought about by a dose of MTX which prolonged the survival of an allogeneic skin graft by only two days (11). MTX can also condition an adult animal so that it acquires immunologic tolerance of allogeneic neoplasms (43). The tolerance was induced by a treatment consisting of MTX and a suspension of non-neoplastic allogeneic cells. Following this, the animals received tumor cells from the strain donating the initiating suspension of cells. When donor and recipient shared the same H-2 allele, 15/15 mice acquired specific tolerance of the malignant graft. 6-MP has also been shown to abrogate immunity to tumor allografts in experimental animals (17), but, more seriously, the purine analog azathioprine has apparently suppressed the rejection of allogeneic cancers in man. These extraordinary cases involve the transplantation of an H-2 alíele, 15/15 mice acquired specific tolerance of the parental strain to the Shope fibroma antibodies. Circulating antibodies may not, however, occur; 6-MP (20) and MTX (3) have a similar effect. These two compounds also sharply diminish the formation of antifibroma antibodies. Circulating antibodies may not, however, be the sole factors responsible for fibroma regression because the administration of hyperimmune serum to MTX-treated rabbits failed to cause regression of tumors. A delayed hypersensitivity mechanism could be important in halting the spread of this neoplasm, and it is of some interest that MTX completely blocked delayed type reactions to the Shope fibroma virus (3). Another possible example of enhancement of the growth of an autochthonous neoplasm by an immunosuppressive drug was recently disclosed (9). Newborn mice of the C57BL strain were given four injections of 6-MP and, after a latent period of five months, 29% had developed a lymphoma. The mechanism of this phenomenon is unknown and a number of possibilities will have to be considered; nevertheless, it is conceivable that the inhibitory effects of the antimetabolite on immunity was connected with the high incidence of neoplasms in these animals.

It is naturally tempting to relate these findings in experimental animals to the problem of cancer in man, but, however alluring this may be, any such analogies would not be supported by presently available data. By and large, experimentally induced neoplasms are well-defined, readily studied systems; in comparison, spontaneous malignancies in man are not understood at all. There is, for example, little convincing evidence that immune mechanisms modulate the growth of human tumors, and until this is demonstrated it would be unwise to leap to far-reaching conclusions regarding the immunosuppressive properties of anticancer drugs. There is also the fact that not all compounds with antitumor activity are immunosuppressive. Uracil mustard is a good example of this, since it does not inhibit antibody synthesis in the rat when given doses sufficient to inhibit the growth of the Walker 256 tumor (8). Furthermore, even though inhibition of immunity occurs in patients treated with these agents there is usually a powerful antitumor effect as well. Thus, a balance of forces must interplay: suppression of immunity and suppression of neoplastic growth. At least from the clinician's point of view, the second-named force is the immediate observable effect which benefits his patient. Whether or not the immunosuppressive effect could be responsible for the usual recurrence and continued growth of the neoplasm is simply unknown. All that can be done now is to provide a climate for considering the validity of the hypothesis mentioned earlier in the event that immune mechanisms are of demonstrated importance in determining the course of human neoplasms.

REFERENCES


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