CANCER BIOTHERAPY & RADIOPHARMACEUTICALS
Volume 13, Number 2, 1998
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EDITORIAL

Treatment of Drug Resistance: Biotherapy or Chemotherapy?

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Biotherapy has been classically defined as the use of biological substances, generally derived from protein or peptide products of the human genome for the treatment of human diseases. A broader definition encompasses all biologically derived materials, including products of bacterial fermentation, substance from the soil and sea, as long as the substance was derived from a natural biological source. Chemotherapy has been classically defined as the utilization of small compounds, sometimes extracted but generally synthetic, utilizing molecules of a defined nature not normally present in the human body. However, there is overlap between the two as can be seen from these definitions. Molecules originally derived from natural sources are later produced synthetically, either wholly or in fragments, which are then more akin to classical chemicals synthesized for chemotherapy.

There is now a whole new field of genetic manipulation that falls within the field of biotherapy, except that some of the modulators of genetic function are chemical in origin. Thus, when we have a small chemical that modulates gene function, resulting in the over- or under-production of a particular protein coded by that gene, is it chemotherapy or biotherapy? In this area one could place the current research having to do with drug resistance, which appears to be largely modulated by natural gene products which code for proteins causing cells to exhibit multiple drug resistance (MDR).

There now exists a whole series of compounds from Verapamil to Cyclosporin and its derivatives to unique other compounds such as CBT -1, which appear to modulate drug resistance by reducing the expression of P-glycoprotein coded for by the gene MDR-l. Since this glycoprotein functions as part of the membrane "pump" which can affect intracellular levels of certain chemotherapy drugs such as the anthracyclines, the taxanes, the vinca alkaloids and the epipodophyllotoxins, this maybe a very important form of biomodulation that could have important effects on the sensitivity of cancer cells to classical chemotherapy drugs. Such an approach is illustrated by the CBT -1 article in this issue and the literature described in that article and the references. There is now considerable evidence that selected chemical substances can change the expression of P-glycoprotein and make cells more sensitive to chemotherapy in vitro and in vivo. These substances may well be even more important in the prevention of the development of MDR by cancer cells that are sensitive to chemotherapy, as opposed to attempting to reverse a previously established pattern of drug resistance, whether natural or

acquired. Research in this area is at the Phase n level for existing compounds and there are a whole series of other compounds and derivatives which are still in pre-clinical testing and early Phase I trials.

A reverse form of genetic manipulation is also being attempted with the insertion of MDR-l into normal cells (bone marrow precursors) to make the bone marrow less sensitive to chemotherapy by inducing the expression of P-glycoprotein and "protecting" bone marrow cells from the adverse effects of chemotherapy. Phase I trials with this approach are currently underway.

Finally, a whole series of mechanisms are becoming available to insert genes and to alter existing genes in individual cells to change the expression of these genes through their protein products. Are all of these manipulations forms of biotherapy? In the broadest sense it would seem so even though the final result of such manipulations may be to make cancer cells more sensitive to chemotherapy. Thus, we have surgery which is reasonably a pure modality of cancer therapy, although biological substances are now being used to guide surgeons (labeled monoclonal antibodies to determine the extent of cancer to be resected). Thus, even surgery is being "biomodulated." In radiation therapy, the second modality of cancer treatment, cell sensitivity to radiation therapy can be altered by chemical and biological substances and ultimately by gene manipulation, giving a form of biomodulation for radiation therapy. The biomodulation of chemotherapy has been discussed above and more "pure forms" of biotherapy are being extensively evaluated. Thus, while there are four forms of cancer treatment; surgery, radiotherapy, chemotherapy and biotherapy; there are increasing interactions between these approaches more complicated than simply adding one to another (multi- modality therapy). These forms of biomodulation have their basis in biotherapy which continues to enhance the effects of the three classical modalities of cancer treatment, as well as being an increasingly effective treatment modality in its own right.