Preliminary Therapeutic and Localization Studies with Human Chorionic Gonadotrophin

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Abstract

Studies in both patients and mice have been carried out using heterologous antibody directed at secreted products of tumors. In preliminary therapeutic studies in patients with drug-resistant choriocarcinoma and malignant teratoma, heterologous anti-human chorionic gonadotrophin (HCG) and anti-a-fetoprotein have been combined with continued cytotoxic chemotherapy. The results to date, although interesting, are inconclusive. In nude mice, anti-HCG administration at the time of inoculation with choriocarcinoma cells failed to inhibit tumor growth.

\[ ^{131}\text{I}-\text{Labeled anti-HCG and anti-carcinoembryonic antigen have been used in localization studies. Specific:non-specific ratios of up to 2:1 were obtained in human and murine studies with HCG- and carcinoembryonic antigen-producing tumors.} \]

Our studies with HCG as a marker for radioimmune localization of tumor sites are at a very preliminary stage, but some of our earlier studies have a bearing on the theme of this workshop. In fact, we attempted radioimmunolocalization of a pulmonary metastasis of choriocarcinoma in 1973, using \( ^{125}\text{I} \)-labeled anti-HCG, but the negative results discouraged active pursuit of this problem.

The ability to discriminate between HCG and luteinizing hormone depends on the carboxy-terminal "tail" of the \( \beta \) subunit. Immunoreactive HCG is now known to be produced at various sites in the normal subject and, in addition to its synthesis on a large scale by gestational and teratomatous trophoblastic tumors, perhaps 10 to 15% of all tumors synthesize this glycoprotein in amounts detectable by present radioimmunoassay methods (3).

Although gestational choriocarcinoma is, despite early metastasis, one of the most successfully treated human cancers, prognosis depends on the capacity of the tumor to become drug resistant. A wide range of drugs is used in intensive protocols, but some cases still prove resistant, usually at a stage where the tumor has been reduced to a very small mass and is often undetectable by conventional means. Residual masses, as demonstrated radiologically, may or may not contain viable tumor. The challenge here then is to find an alternative approach to localize or eradicate the small foci of residual viable tumor cells revealed by low serum concentrations of HCG.

In the late 1950's and 1960's, we extensively applied active immunization procedures without notable success (1).

We also reported (2) that rabbit anti-HCG was highly cytotoxic to trophoblastic cells in culture and that cytotoxicity was complement dependent. Since then, 7 patients with multi-drug-resistant gestational or teratomatous choriocarcinoma have received antibodies to HCG from rabbits or sheep at a time when their tumors were resistant to chemotherapy. These clinical studies have not been decisive in that the antibody, in an amount equal to 200 to 300 ml of antiserum by i.v. infusion over 24 hr, has been followed, or accompanied by, cytotoxic chemotherapy. Four of the 7 patients have achieved sustained remission when it seemed very unlikely that they would do so with chemotherapy alone.

Attempts to treat nude mice bearing recently inoculated BeWO line choriocarcinoma cells by anti-HCG alone have, however, proved unsuccessful. Although this failure may be due to ineffective complement action, these studies as a whole must still be regarded as unproven. Some of the individual cases did, however, suggest that an antitumor effect was obtained, and we are now attempting to determine the factors controlling the distribution of such antibodies in the extracellular fluids and on cell membranes.

In general then, the challenge is one which we can anticipate will become more common as chemotherapy approaches tumor eradication for a wider range of tumors. That is, we see patients who initially have an extensive tumor burden at widely scattered metastatic sites, and this may be reduced by 4 to 5 logs, but then, when the patient has a relatively small burden, of the order of say \( 10^5 \) to \( 10^7 \) cells, resistance is encountered. Detection of residual tumor masses, identifiable radiologically, may fail to reveal any viable tumor at that site, or it may reveal a few microfoci of viable cells.

We can consider an example of this situation in which a patient with an initial HCG concentration of 200,000 mill/ml responded well, went into apparent remission after 6 months of treatment, and then relapsed 3 months after discontinuing therapy. Further chemotherapy reduced the serum HCG to between 1 and 10 mill/ml, which indicated that there was persisting minimal HCG activity. A chest radiograph at that time showed a dubious opacity in the right lung field, but computerized tomography revealed 2 lesions.

The patient was therefore given 500 \( \mu \)g sheep anti-HCG \( \gamma \)-globulin labeled with \( ^{131}\text{I} \) (1.25 mCi). It was shown that labeling of the antibody had caused no significant reduction of antigen binding. A total of 300 \( \mu \)Ci of the labeled preparation was given i.v. Forty % of the counts were excreted in urine in the first 24 hr. Scanning, however, failed to reveal any localization at 48 hr postinjection. Thoracotomy was performed on Day 3. The 2 lesions were dissected out, and microscopy revealed a small focus of viable choriocarcinoma cells in otherwise necrotic tissue in Lesion A but no viable cells in necrotic Lesion B. The 2 lesions were counted in well counters and gave 7,600 cpm/g in Lesion A with 6,400 cpm/g in Lesion B. Against a serum background of 60,200, the difference between the 2 lesions is not significant. Clearly, much better discrimination will be re-

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1. Presented at the UICC Workshop on Radioimmunodetection of Cancer, July 19 to 21, 1979, Lexington, Ky.
2. The abbreviation used is: HCG, human chorionic gonadotrophin.
quired if localization techniques are to make a useful contribution to this sort of problem for which we already have a good tumor marker.

In addition, one of the authors (J. Lewis) has started experimental studies with choriocarcinoma (BeWO cells and a new line of choriocarcinoma) growing in nude mice. BeWO cells proliferate rapidly in nude mice on first inoculation from culture so that tumors of 1 to 2 cm diameter are produced in 14 to 21 days. Isotopically labeled rabbit anti-HCG can be readily demonstrated to be taken up in these lesions by external scanning, but nonspecific rabbit IgG is also taken up demonstrably. In general, the ratio of specific to nonspecific immunoglobulin uptake has not exceeded 2:1 in our hands.

We have, incidentally, obtained positive scans in a small group of patients with carcinoembryonic antigen-producing epithelial tumors given isotopically labeled anti-carcinoembryonic antigen. However, our view is that we should be very cautious in our interpretation of these data. The level of background counts due to activity in blood is uncomfortably high in relation to the level detectable in target tissues. Further, much more work is needed to show whether the specific:nonspecific uptake can be improved. Nevertheless, it is an approach which we feel now must be thoroughly explored.

References

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