Intralymphatic Immunization: Current Status

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Abstract—A progress report and the research plan for a new method of antitumor immunization using the intralymphatic route are presented. A total of 205 intralymphatic infusions of intact cellular vaccines have been performed in normal and tumor-bearing dogs. In vitro and in vivo experiments on normal dogs demonstrated that intralymphatic immunization produces a more rapid and more intense cytotoxic cellular immune response compared to the subcutaneous route. Experiments in tumor-bearing dogs showed reduction or stabilization of tumor mass after intralymphatic infusion of irradiated malignant cells. These data indicate that intralymphatic immunization may be the method of choice for stimulating strong cellular immune responses to weakly immunogenic materials.

INTRODUCTION

The first attempt of antineoplastic intralymphatic immunostimulation by infusion of presumably immunogenic material (irradiated autochthonous tumor cells) was performed on September 8, 1972 on a 75-yr-old patient with disseminated melanoma. Three consecutive infusions via the same afferent lymphatic vessel were done 3 and 4 days apart. During subsequent weeks, all metastases continued to grow with the exception of a nodule of the right thigh which was in the infused area. The patient expired 3 weeks later.

This attempt in a human patient, which was made under exceptional circumstances, stimulated further investigation of the intralymphatic route of immunostimulation as a potentially effective mode of antitumor immunotherapy. However, since neither the benefits nor hazards of this method were known, it was not appropriate to proceed further in humans without undertaking relevant preclinical experiments on animals. Such studies have been in progress since January of 1974 in the Division of Radiation Therapy at UCLA [1, 2, 3].

MATERIAL AND METHODS

All experiments have been done on randomly-bred normal and tumor-bearing dogs which were selected for the following reasons:

1. Dogs develop spontaneous malignant tumors that are similar to human malignancies.
2. Injection via the intralymphatic route is technically almost as easy as it is in humans.

Standard lymphangiography techniques were used for cannulation and infusion of the extremities.

RESULTS

1. Experiments on normal dogs

Differential immune responses to immunogenic material injected intralymphatically, subcutaneously, or intradermally have been studied on 22 normal, weight-matched dogs.

Evaluation of immune responses to a malignant cell vaccine. Direct cell-mediated cytotoxicity, complement-dependent antibody cytotoxicity, and skin test reactivity to a xenogeneic leukemia cell line was serially assessed in 16 dogs divided into 4 groups which had received respectively:

—Intralymphatically, a suspension of \(10^6\) leukemia cells.
—Intralymphatically, medium only.
—Subcutaneously, \(10^6\) leukemia cells.
—Subcutaneously, medium only.

Results of both primary and secondary immunizations showed that cell-mediated
immune responses were preferentially accelerated and significantly greater in the groups which had received leukemic cells intralymphatically.

Evaluation of responses to BCG. In this study, 2 groups of 4 dogs received respectively BCG (Glaxo) intradermally and intralymphatically. The responses were evaluated clinically by tuberculin skin testing, and the sera were serially sampled to assess antibody against BCG.

All dogs which received the BCG intralymphatically developed large regional lymphadenopathies which persisted for several months. Two dogs in the "intralymphatic" group developed positive skin tests at 11 and 23 days, and skin test became positive at 45 days in the "intradermal" group. The level of antibodies is not known yet; all the sera will be assessed at the same time.

2. Experiments on tumor-bearing dogs

A. Randomized study of Stage III malignant lymphomas was undertaken in which one group (7 cases) received intralymphatic infusions of irradiated autochthonous tumor cells. The second group (4 cases) received intralymphatically the medium only.

The lymphadenopathies have been found to routinely decrease in size at least temporarily in Group 1 but continue to grow progressively in Group 2. Thus far, the mean survival is $42 \pm 30$ days in Group 1 and $13 \pm 6$ in Group 2.

B. Nonrandomized study of intralymphatic immunization in solid tumors:

1. Irradiated autochthonous, allogeneic, or xenogeneic tumor cells were repeatedly infused via the intralymphatic route in:
   - Two cases of pulmonary metastasis from breast adenocarcinoma;
   - Two cases of pulmonary metastasis from soft tissue sarcoma;
   - One case of epidermoid carcinoma of the upper respiratory tract.

All cases showed reduction or stabilization of tumor mass.

2. BCG was administered intralymphatically in 2 cases of melanoma. Both cases expired within 10 days of the first infusion with fulminant tumor growth.

DISCUSSION

From these studies involving 205 intralymphatic infusions in 41 dogs, the following points can be made:

1. The intralymphatic route of administration not only is technically applicable but can be used repetitively if necessary. Up to 9 infusions at the same site have been performed over a 5-month period in the same animal.

2. No side effects, including anaphylactic or allergic reactions, have been observed following intralymphatic injection of autochthonous, allogeneic, or xenogeneic tumor cells.

3. Cellular immune responses are quantitatively greater following intralymphatic immunization than the ones elicited by the subcutaneous immunization.

4. A reduction or stabilization of tumor size has always been observed after intralymphatic infusion of irradiated tumor cells.

5. These tumor reductive responses are not due to a direct toxic effect since they were observed in remote areas (pulmonary metastasis, carcinoma of the upper respiratory tract, distant lymphadenopathies).

CONCLUSION

Our findings indicate that intralymphatic injections may be the route of choice for the immunotherapeutic administration of weakly immunogenic cellular materials and that no adverse side effects or complications have thus far been associated with this method of immunostimulation.

REFERENCES

