ADVANCES IN CANCER RESEARCH

Volume 14

ADVANCES IN CANCER RESEARCH

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ACTIVE IMMUNOTHERAPY

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I. Introduction

Specific active immunotherapy is defined as the stimulation of immune reactions directed against tumor-associated antigens; nonspecific active immunotherapy is the general stimulation of the host's immune reactions by "adjuvants" of immunity.

There is an extensive literature on experimental immunological prevention, describing experiments in which the antitumor effects of immunization (Glynn *et al.*, 1963; Mathé *et al.*, 1969b) or stimulation of immune reactions (Old *et al.*, 1959; Biozzi *et al.*, 1960; Amiel, 1967; Mathé *et al.*, 1969b) have been tested by carrying out these procedures prior to grafting or inducing a tumor. On the other hand, far less attention has been paid to immunotherapy, the objective of which is to devise immunological procedures to inhibit established tumors. Immunotherapy is applicable to man at present, while our knowledge of tumor associated antigens in man is far too small to warrant any attempts at tumor prevention.

One of the main reasons for the paucity of experiments on specific immunization after grafting or inducing a tumor can be found by analogy between cancers and infections, against which immunotherapy is no longer used in a curative role. However, it now seems that when immunotherapy is used to cure cancer, it can sometimes be efficacious, though this varies according to different circumstances; but occasionally remarkable effects have been observed in several experimental systems and have already shown to act in man.

This review will be limited as far as possible to a consideration of isogenic tumors grafted into hosts with identical histocompatibility antigens, or autologous tumors, either induced by carcinogens or which occur spontaneously. Only passing reference will be made to studies on tumor grafted into incompatible hosts.

Clinical trials have often preceded studies in experimental animals or have been made at the same time. We made our first clinical trial of immunotherapy in acute lymphoblastic leukemia in 1964. Provided these trials are carried out in a scientific fashion, their results can be just as valuable as experiments in animals. However, the results of clinical and experimental studies will not be mixed in this article, but will be described consecutively.

II. Experimental Basis

A. Specific Immunotherapy

Various antigenic stimulants can be used for specific immunotherapy, namely tumor cells, purified antigens, or oncogenic viruses.

1. *Tumor Cells*

In mice, grafted subcutaneously with 10^4 L 1210 leukemia cells, a significant increase of survival time has been obtained by injecting them 24 hours or even 4 days after grafting, with 10^7 isogenic leukemic cells irradiated with 15,000 rads *in vitro* (Mathé 1968; Mathé *et al.*, 1969b) (Fig. 1). In these experiments tumor cells had been injected subcutaneously, and the leukemia had been transmitted over so many generations that it might have produced a certain withdrawal of histocompatibility with the mice to which it had been grafted (the latter were Fl(DBA/2 $\times$ C57Bl/6) mice).

Two other experiments were made in which we treated mice, inoculated intravenously with 10^4 living cells of very recently induced leukemias. The RC19 leukemia, induced by Rauscher virus, and the E ♀ Kl leukemia, induced by Gross virus in C57Bl/6 mice were used. Specific active immunotherapy applied 24 hours after an isogenic graft of E ♀ Kl leukemia had a noticeable effect (Mathé *et al.*, 1971). Iris

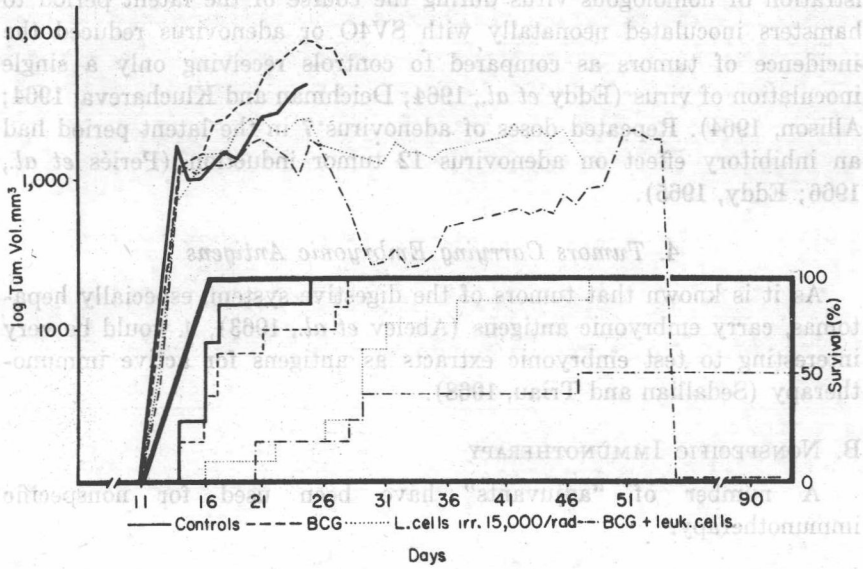

FIG. 1. Tumor volume and cumulative survival of mice grafted with L 1210 leukemia and not treated or treated by BCG (first injection 24 hours after the graft and injections repeated each 4 days), or irradiated leukemic cells (one injection 24 hours after the graft), or association of both.

Parr (1971) obtained similar results on 5178Y tumor grafted intraperitoneally with 10^4 live tumor cells.

Kronman *et al.* (1970) obtained remarkable results in pure strain guinea pigs in which they had grafted hepatomas intramuscularly. Intradermal injections of living hepatoma cells (three injections per week on alternate weeks) induced an immunological reaction against the hepatomas.

2. *Purified Antigens*

Though several groups of chemists are now working on the extraction and characterization of "tumor-associated antigens," up until now they have only been testing their value in preventing the take of tumors. In our laboratory, Martyré and Halle-Pannenko (1968) have been working along these lines studying the antigens of the virus-induced Charlotte Friend leukemia.

3. *Vaccination by Oncogenic Viruses*

Even when the vaccination is commenced after the inoculation of the animal with the virus to induce a tumor, an antitumor effect can be achieved during the latent period. It has been shown that the admin-

istration of homologous virus during the course of the latent period to hamsters inoculated neonatally with SV40 or adenovirus reduced the incidence of tumors as compared to controls receiving only a single inoculation of virus (Eddy *et al.*, 1964; Deichman and Kluchareva, 1964; Allison, 1964). Repeated doses of adenovirus 7 in the latent period had an inhibitory effect on adenovirus 12 tumor induction (Periés *et al.*, 1966; Eddy, 1965).

4. *Tumors Carrying Embryonic Antigens*

As it is known that tumors of the digestive system, especially hepatomas, carry embryonic antigens (Abelev *et al.*, 1963), it would be very interesting to test embryonic extracts as antigens for active immunotherapy (Sedallian and Triau, 1968).

B. Nonspecific Immunotherapy

A number of "adjuvants" have been used for nonspecific immunotherapy.

1. *Freund's Adjuvant*

Freund's adjuvant is the classical example of a stimulant of immunity (Freund, 1953). It has only rarely been used to try to cure tumors; that is, given after the establishment of the tumor. Hirano and his colleagues (1967) described how this adjuvant given 1 week after animals had been grafted with a lymphoma inhibited the tumor growth.

Allison (1964) observed that giving Freund's complete adjuvant to hamsters during the latent period following neonatal inoculation with adenovirus type 12 affected tumor production and the production of complement-fixing antibodies to adenovirus virions and T-antigens.

2. *Zymosan*

Zymosan, first used as an immunosuppressive agent (Mathé and Bernard, 1956), was later shown by Bradner *et al.* (1958) to be able to stimulate antitumor immunity and has been used to attempt to cure various nonspecific grafted tumors (Sokoloff *et al.*, 1961) as well as spontaneous tumors (Martin *et al.*, 1964). Under certain conditions, which are described later, it can have a beneficial effect.

3. *BCG*

BCG has been shown in our laboratory to prolong slightly the survival of mice carrying L 1210 leukemia, when it is injected 24 hours after a graft of 10^4 leukemic cells (Mathé, 1968; Mathé *et al.*, 1969b). Better