BCG in the Treatment of Human Cancer

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It is a tribute to the astute observations of clinicians and researchers, and an example of the unpredictability of science and medicine, that Bacille Calmette-Guérin (BCG), an anti-tuberculosis vaccine introduced in 1921, should in 1975 be under extensive investigation for its possible role in the treatment of human cancer.1 The history of BCG’s use as a potential cancer treatment is worth reviewing. For more than 100 years, the miraculous disappearance of cancer after severe infection has occasionally been reported. Examples of cancer regression subsequent to local infection led Coley to conclude, in the early 1900s, that bacteria released a toxin that could directly or indirectly cause the death of tumor cells. He therefore began to treat cancer patients with various bacterial toxins but, despite a few promising results, found no consistent therapeutic benefit.

Clinical observations, however, continued to support the concept that bacterial infections might play a role in the regression of cancer.2 For instance, a number of investigators noted that following thoracotomy for lung cancer, those patients with postoperative empyema had a significantly better chance for long-term survival than those who did not have empyema. (Fig. 1.) This was a remarkably surprising finding, and one of the few examples I know of where patients benefit from a postoperative complication!

Independently, immunobiologists interested in the nature and control of immune responses to foreign antigens discovered that the simultaneous injection of certain bacteria with an antigen, such as bovine serum albumin (BSA), markedly increased the strength of the immune response against BSA. Tubercle bacilli were found to be among the most effective bacterial adjuvants for immune stimulation. Finally, with increased understanding of the immune system’s role in cancer, experimental immunologists began to question whether BCG or other types of “immunoadjuvants” would be of value in stimulating the immune system to destroy tumor cells in animals or man.

Methods of Administration

Intrallesional

In about 90 percent of cases, BCG injected into the skin nodules of metastatic melanoma causes an inflammatory reaction at the injection site and regression of local disease.3 Occasionally untreated nodules also disappear, but they are generally close to the injected nodule or within the same lym-
of the 34 controls who had surgery without empyema were alive. Ruckdeschel, J.C.; Codish, S.D.; Stranahan, A., and McKneally, M.F. Postoperative empyema improves survival in lung cancer. Documentation and analysis of a natural experiment. New Eng J Med. 287: 1013-1017. 1972.

A clinical trial of preoperative BCG for patients with primary melanoma and a poor prognosis should contact: Dr. Steven A. Rosenberg, Chief, Surgery Branch, National Cancer Institute, Building 10, Room 10N116, Bethesda, Maryland 20014. Telephone: 301-496-4164.

The use of BCG in the treatment of melanoma has, thus far, been restricted to patients with metastatic disease. However, its ability to eradicate local manifestations of disease in man and animals has led to the logical conclusion that injection of BCG into primary melanomas prior to surgical treatment might also prove beneficial. A clinical trial of preoperative, intralesional...
BCG, in patients with primary melanoma and a poor prognosis has been started by the National Cancer Institute. (See page 199.)

Paralesional

Experimental studies have shown that BCG may be most effective if deposited in or on tumor cells, and various techniques are now being tried for inaccessible tumors. In an attempt to bring BCG into contact with residual microscopic disease, some postoperative lung cancer patients now receive BCG by aerosol inhalation. In addition, BCG has been intentionally introduced into the pleural space subsequent to lung resection in order to reproduce the beneficial effects of postoperative empyema. However, it is still too early to fully evaluate the clinical value of these approaches.

It is important to note that all local or paralesional methods of administration also lead to systemic distribution of BCG. Following the intralesional injection of BCG, bacteria have been recovered from venous blood at distant sites, and patients receiving BCG by these methods may develop granulomatous hepatitis.

Systemic

The systemic administration of BCG has also been studied, as many cancers are already disseminated by the time of diagnosis or are systemic from inception. In patients with leukemia and other disseminated cancers, BCG is applied to the skin either by scarification (Fig. 2.) or by a multiple puncture device such as a Heaf gun. (Fig. 3.) In scarification, the skin is vigorously scratched with a needle and BCG applied to the open wound; in the latter method, BCG is spread on the skin and...
introduced systemically by multiple intradermal punctures.

Three trials of BCG combined with chemotherapy in the treatment of acute myelogenous leukemia of adults can now be evaluated. In all three instances, a positive effect has been noted.\(^4\)\(^6\) Although the number of patients studied is still small, there has been a significant prolongation in the duration of remission and survival. (Table.) The mechanisms by which BCG causes a beneficial effect in acute myelogenous leukemia is not yet known, but whatever the mechanism, these studies do demonstrate the efficacy of BCG in human cancer.

Oral
It has been clearly demonstrated that patients with negative tuberculin skin tests can be converted to positive skin tests following oral administration of BCG. Several trials of oral BCG therapy for cancer are now in progress, but results are not yet available.

**Mechanisms of Action**
Why does the injection of BCG cause a tumor to regress and disappear? The answer is not entirely clear. It is known, however, that BCG induces a local, sustained, chronic granulomatous inflammatory response. Lymphocytes, macrophages and a variety of polymorphonuclear cells are attracted into the site of injection, and an immune response against the BCG organism is initiated. As part of the lymphoid response, various types of cytotoxic substances are released and all cells in the immediate vicinity—tumor as well as normal cells—may be damaged or destroyed. In addition, macrophages, activated into a state of increased phagocytic and metabolic function, seem able to kill tumor cells by as yet unknown mechanisms. Thus, either as the result of activated macrophages or through the local release of cytotoxic materials, tumor cells may be killed as "innocent bystanders" at the site of an intratumoral injection of BCG.

It is assumed that the systemic administration of BCG will stimulate the immune system to heightened activity, and increase the intensity of low-level antitumor immune responses leading to

| Trial | Number of Patients | Estimated Median Remission Duration (Weeks) | Estimated Median Survival (Weeks) |
|-------|--------------------|---------------------------------------------|----------------------------------|
| Powles\(^4\) | | | |
| Immunotherapy & Chemotherapy | 30 | 44 | 74; \(p = 0.01\) |
| Chemotherapy | 22 | 27 | 39 |
| Vogler\(^5\) | | | |
| Immunotherapy & Chemotherapy | 18 | 39.4; \(p = 0.002\) | 84.2; \(p = 0.005\) |
| Chemotherapy | 23 | 26 | 70.4 |
| Gutterman\(^6\) | | | |
| Immunotherapy & Chemotherapy | 14 | > 72; \(p = 0.04\) | Too Early |
| Chemotherapy | 21 | 60 | |
tumor cell destruction, wherever such cells may be located. However, it must again be emphasized that these explanations are speculative, and the actual mechanisms involved are not fully understood.

Evaluation of Clinical Trials
The potential value of BCG in the treatment of a variety of cancers is presently under extensive investigation. Several years will be required before all the results can be evaluated. This is a very difficult task indeed, as BCG is a living organism, grown in culture and subject to mutational changes over time, as are other rapidly dividing organisms. In addition, since its mechanisms of action are unknown, it is impossible to monitor BCG cultures and detect mutations that might make subsequent generations less effective for immunotherapy. Moreover, there are many different substrains of BCG; Pasteur Institute BCG differs in many ways from "Glaxo" BCG. To further complicate matters, preparations vary in the number of living BCG organisms, the ratio of living to dead organisms, and a variety of other more subtle factors, all of which may have a bearing on the therapeutic efficacy of the material. In consequence, otherwise identical trials may produce different results.

For these reasons, efforts are now under way to develop nonliving derivatives of BCG, materials that can be purified and chemically analyzed so that uniform, chemically defined substances, which lack the disadvantages of BCG, can be used for future clinical trials. As a step in this direction, immunotherapeutic trials of MER, a rather crude methanol extractable residue of BCG, are currently in progress. Other nonliving derivatives of tuberculosis organisms are also being prepared. In a few years, a whole alphabet soup of chemically defined substances will most probably be available to replace BCG.

Public interest in the Maruyama vaccine, a water soluble extract of human tuberculosis organisms that has been studied in Japan, has recently been aroused by a sensational and largely inaccurate newspaper article. This vaccine has no demonstrable effect against animal tumors and has never been studied in man by either a randomized, controlled or blind trial. Exaggerated reports of its value must now be tempered by the less well-publicized studies of physicians who have found it ineffective in the treatment of their cancer patients. At present, the Maruyama vaccine must be considered as one of the very large number of "unproven cancer remedies." It seems most unlikely that this vaccine, if it has any activity at all, will be more effective than BCG which has been proven therapeutic in many animal tumor systems, as well as in melanoma and acute myelogenous leukemia in man.

Hazards and Complications
Until chemical substitutes for BCG are developed, the administration of tubercle bacilli poses several problems. Severe fever, an influenza-like syndrome, hepatic dysfunction and granulomatous hepatitis have all been reported. Several deaths have also occurred. In animal model systems, the use of BCG as a treatment for cancer has occasionally (but rarely) led to an

BCG IS AN EXPERIMENTAL THERAPEUTIC AGENT
BCG has now been under clinical investigation as a cancer treatment for more than 10 years. While BCG can be readily obtained for use as an antituberculosis vaccine, it has not been cleared by the Food and Drug Administration as a cancer treatment agent, and can only be obtained under an Investigational New Drug (IND) clearance as an experimental agent.
IMMUNOTHERAPY REGISTRY
To assist physicians in selecting institutions for patient referral, an Immunotherapy Registry has been established by the National Cancer Institute. Information concerning the type of cancer being studied, the type of immunotherapy used, and the institution where the trial is in progress can be obtained by contacting: Dr. Dorothy Windhorst, Director, International Registry of Tumor Immunotherapy, National Cancer Institute, Building 10, Room 4B17, Bethesda, Maryland 20014.

unexpected increase or "enhancement" in the rate of tumor growth. There have been no clear-cut cases of enhancement following BCG treatment of cancer in man. All of these findings, however, should emphasize that BCG treatment is not without hazard and should now be undertaken only by physicians with appropriate training and experience.

Conclusions
BCG is one of a large number of agents under study as possible immunostimulants and, in turn, represents only a small segment of the rapidly developing field of immunotherapy. By and large, immunotherapy is now and will continue to be used as part of the combined modality approach to cancer treatment. Immunotherapists are working closely with surgeons, radiotherapists and chemotherapists to optimize the potential benefits to the patient. However, many serious problems interfere with the immediate achievement of this goal. Chemotherapy and radiotherapy frequently have a markedly suppressive effect on immunologic function, and even surgery is followed by a period of relative immunosuppression. Detailed studies on the type and duration of immunologic reactions will be required before optimal, multimodality therapy can be designed.

For at least the next several years, clinicians must consider all forms of immunotherapy of cancer as experimental, and not as established treatments. Appropriate patients should be referred and placed as soon as possible in centers where clinical trials are in progress. To assist physicians in patient referral, an Immunotherapy Registry has been developed by the National Cancer Institute.

Results of immunotherapy trials in man and other animals have indicated that the immune system usually makes an effective response against cancer only when the tumor burden is relatively small. This necessitates that immunotherapy be studied in patients with relatively early cancers. Referring patients with early, small tumors to specialized centers assures that adequate numbers will be entered into clinical trials of BCG or other agents, helping to speed the day when immunotherapy will become an integral part of the treatment of human cancer.

References
1. Bast, R.C., Jr.; Zbar, B.; Borsos, T., and Rapp, H.J.: BCG and cancer. New Eng. J. Med. 290: 1413-1420, 1974.
2. Ruckdeschel, J.C.; Codish, S.D.; Stranahan, A., and McKneally, M.F.: Postoperative empyema improves survival in lung cancer. Documentation and analysis of a natural experiment. New Eng. J. Med. 287: 1013-1017, 1972.
3. Morton, D.L. et al.: BCG immunotherapy of malignant melanoma: summary of a seven-year experience. Ann. Surg. 180: 635-643, 1974.
4. Powles, R.L. et al.: Immunotherapy for acute myelogenous leukemia. Brit. J. Cancer 28: 365-376, 1973.
5. Vogler, W.R., and Chan, Y.: Prolonging remission in myeloblastic leukemias by tice-strain Bacillus Calmette-Guérin. Lancet ii: 128-131, 1974.
6. Gutterman, J.V., et al.: Chemoimmunotherapy of adult acute leukemia. Prolongation of remission in myeloblastic leukemia with BCG. Lancet ii: 1405-1409, 1974.
7. Sparks, F.C. et al.: Complications of BCG immunotherapy in patients with cancer. New Eng. J. Med. 289: 827-830, 1973.
8. McKhann, C.F. et al.: Immunotherapy of melanoma with BCG: two fatalities following intralesional injection. Cancer, in press.