B. C. G. — FROM TUBERCULOSIS TO CANCER

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Summary

Modern information on tumor immunology has prompted the use of B. C. G. in the control of tumor growth. Traditionally employed in the past as an antituberculosis vaccine, B. C. G. appears to have been realized as an important therapeutic measure in the treatment of certain tumors, both in animals and humans. The possible mechanisms of action and its untoward effects are outlined.

Since its introduction in 1921. Bacilli Calmette Guerin (BCG) has been tradionally employed as an antituberculosis vaccine. Of late, it has been used in the immuno-prophylaxis of allied conditions like leprosy with some success. Now after five decades of its initial use, it is indeed, surprising that BCG is the subject of extensive investigation for its possible role in the treatment of cancer. Immunological studies in experimental cancer revealed that reticuloendothelial stimulation could check the tumor growth[1]. A number of bacterial adjuvants including the tubercle bacillus were known to be effective immunostimulants[2]. This prompted many investigators to employ BCG for its possible beneficial effect on tumors.[3,4] Several experimental and clinical studies have since been carried out and the subject is briefly reviewed herein.

In experimental animals, the efficacy of BCG appears to be dependent on various factors viz, the dose, the time and route of administration, the tumor load and the host's ability to develop an immune response to mycobacterial antigens.[5-13] Immunosuppression with antilymphocytic serum, thymectomy, irradiation or corticosteroids retards the effect of BCG.[14] Host's ability to show an immune response to tumor associated antigens also seems to be important.[15] At times, pretreatment with certain hydrolytic enzymes viz, neuraminidase derived from vibrio cholerae or with mitomycin C has been shown to enhance the immunogenecity of tumor cells.[16] For some strange reasons BCG immunotherapy proves more effective at certain sites than others.

Thus it appears that BCG immunotherapy proves most effective against small tumor load in host with an intact immune system. However, successful results have also been obtained in instances of larger tumors or metastases with BCG in combination with chemotherapy, endocrine ablation, radiation therapy or surgical removal of the primary tumor.[17,18,19]

In humans, BCG has been mostly employed under two cirumstances viz. in cases of clinically apparent skin cancers and in advanced cases of internal

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malignancies having either metastases or residual tumors from unsuccessful surgical, radiation or chemotherapy. BCG has been used alone or in combination with chemotherapy. Malignant melanoma, basal cell epithelioma, squamous cell carcinoma, mycosis fungoides, lymphangiosarcoma, Kaposi's sarcoma and secondary cutaneous metastases from breast and colon carcinoma have all been treated with BCG with variable success.[20,21,22] Intralesional injections of BCG or PPD have proved rather effective and an initial oral or intradermal BCG administration appears to have enhanced the therapeutic effect of BCG in these cases. However BCG seems to have little effect on visceral metastases. Donaldson[23] has reported better survival rates in 32 patients with advanced squamous cell carcinoma of the head and neck with a combination of BCG, methotrexate and isoniazide than with methotrexate alone, thereby showing the superior effect of combined therapy.

Of the various tumors, BCG has produced most dramatic and gratifying results in the treatment of metastatic melanomas[24]. In about 90 percent of patients, BCG injected into the nodules of metastatic melanoma caused inflammatory reaction and subsequent regression. In a fewer percentage of patients even the untreated nodules in the near vicinity subsided. Distant or visceral metastases, however did not show any regression. In general tumor regression has been restricted to patients with positive immune response tuberculin.[25] The regression of nodules in the immediate vicinity has been related to a systemic response to tumor associated antigens through mechanisms discussed later. It may, however, be added here that response to tuberculin per se may not be as important Cord factor (trehalose-6-6' dimycolate)-a lipid isolated from mycobacterial cell walls can delay tumorogenesis and it does not induce tuberculin sensitivity.[26] Some recent observations suggest an accelerated tumor growth following BCG injection in the primary lesion of malignant melanoma.[27,28] BCG immunotherapy has also been shown to be successful in acute and chronic leukemias and Burkitt's lympoma. These are of little interest to dermatologists and shall not be reviewed here.

The mechanism as to how BCG inhibits carcinogenesis, suppresses tumor growth and causes its regression is not clear. Various speculations have been made.[29,30] It has been attributed to stimulation of immune surveillance. Carcinogenic agents in addition to induction of mutant clones are known to depress both cellular and humoral immunity. BCG could reverse the immunosuppressive effect of such carcinogens. Tumor cells have recently been shown to possess certain antiphlogistic properties producing chemotactic factor inactivator (CFI).[31] BCG could block this thereby giving a chance to body defenses to deal with the tumor cells. Animals injected with BCG are known to resist certain virus infections and the intravenous injection of tuberculin can stimulate the release of interferon in BCG immune mice. Then, possibly BCG could modify the effect of some carcinogenic viruses in favor of the host. It is also believed that BCG at the site of injection attracts lymphocytes and macrophages in proportions which can effectively deal with the tumor cells in the immediate vicinity. Under circumstances of systemic administration of BCG, the heightened state of immune system thus achieved responds in a fashion to produce antibodies against the tumor associated antigens thereby destroying the tumor cells.

Any new therapy has its complications and so does immunotherapy with BCG. Local extensive ulcerations associated with regional lymphadenopathy have been observed following intralesional injection of BCG.[32] Severe febrile episodes, myalgia, generalized malaise,

granulomatous hepatitis, erythema nodosum, pancytopenia, hypersensitivity reactions including anaphylaxis and even deaths have been reported[33,34]. Undoubtedly, immunostimulation property of BCG opens many new avenues for use in a number of diseases associated with immunosuppression. However, it is not without hazard and should be undertaken with care.

REFERENCES

1. Brander WT, Clarke DA, Stock CC: Stimulation of host mice defense against experimental cancer, Cancer Res, 18 : 347, 1958.
2. Freund J : The mode of action of immunologic adjuvants, Adv Tuber Res, 7 : 130, 1956.
3. Old LJ, Clarke DA, Benacerraf B : Effect of BCG infection on transplanted tumors in the mouse, Nature (Lond) 184 : 291, 1959.
4. Weiss DW, Bonhag RS, De Ome KB : Protective activity of fractions of tubercle bacilli against isologous tumors in mice, Nature (Lond) 190: 889, 1961.
5. Lemonde P, Dubreuil R, Guindon A et al : Stimulating influence of BCG on immunity to polyoma tumors and spontaneous leukemia, J Natl Cancer Inst, 47 : 1013, 1971.
6. Keller R, Hess MW : Tumor growth and nonspecific immunity in rats-The mechanism involved in inhibition of tumor growth, Br J Exp Pathol, 53 : 570, 1972.
7. Finkelstein JZ, Tittle KL, Imagawa DT : Immunoprophylaxis and immunotherapy of leukemia with BCG, Lancet, 2 : 875, 1972.
8. Weiss DW : Nonspecific stimulation and modulation of the immune response and of state of resistance by the methanol-extraction residue fraction of tubercle bacilli, Natl Cancer Inst Monogr, 35 : 157, 1972.
9. Bast RC, Zbar B, Borsos T et al : BCG and cancer-I, New Eng J Med 290 : 1413, 1974.
10. Zbar B, Bernstein I, Tanaka T et al : Tumor immunity produced by the intradermal inoculation of living tumor cells and living mycobacterium bovis (strain BCG), Science, 170 : 1217, 1970.
11. Bartlett GL and Zbar B : Tumor specific vaccine containing mycobacterium bovis and tumor cells-safety and efficacy, J Natl Cancer Inst, 48 : 1709, 1972.
12. Tokunaga T, Kataoka T, Nakamura RM, et al : Tumor immunity induced by BCG-tumor cell mixtures in syngeneic mice, Jap J Med Sci Biol, 26 : 71, 1973.
13. Zbar B, Bernstein ID, Bartlett GL et al : Immunotherapy of cancer regression of intradermal tumors and prevention of growth of lymph node metastases after intralesional injection of living mycobacterium bovis, J Natl Cancer Inst 49 : 119, 1972.
14. Chung EB, Zbar B, Rapp HJ : Tumor regression mediated by mycobacterium bovis (strain BCG)-effects of INH, cortisone acetate and antithymocyte serum, J Natl Cancer Inst, 51 : 241. 1973.
15. Parr I : Response of syngeneic murine lymphomata to immunotherapy in relation to the antigenicity of the tumor, Br J Cancer 27 : 174, 1972.
16. Simmons RL, Rios A : Combined use of BCG and neuraminidase in experimental immunotherapy, Surg Forum, 22 : 99, 1971.
17. Pearson WJ, Pearson GR, Gibson WT et al : Combined chemoimmunostimulation therapy against murine leukemia, Cancer Res 32 : 904, 1972.
18. Piessens WF, Hiemann R, Legros N et al : Effects of BCG infection on residual disease of the rat mammary tumor after ovariectomy, Dur J Cancer, 7 : 377, 1971.
19. Sparks BC, O Connell TX, Lee YTN : Adjuvant preoperative and postoperative immunochemotherapy for mammary adenocarcinoma in rats, Surg Forum, 24 : 118, 1973.
20. Bast RC, Zbar B, Borsos T et al : BCG and cancer-II, New Engl J Med, 290 : 1458, 1974.
21. Klein E, Holterman OA : Immunotherapeutic approaches to the management of neoplasms, Natl Cancer Inst Monogr 35 : 379, 1972.

22. Klein E : Immunotherapy of cancer in man : a reality, Natl Cancer Inst Monogr, 39 : 134, 1973.

23. Donaldson RC : Chemoimmunotherapy for cancer of the head and neck, Amer J Surg, 126 : 507, 1973.

24. Morton DL, Eilber FR, Holmes EC et al : BCG immunotherapy of malignant melanoma : summary of a seven year experience, Ann Surg, 180 : 635, 1974.

25. Morton DL Eilber FR, Malmgren RA et al : Immunological factors which influence response to immunotherapy in malignant melanoma, Surgery 68 : 158, 1970.

26. Bekierkunst A, Yarkoni E : Granulomatous hypersensitivity to trehalose-6-6'-dimycolate (Cord factor) in mice infected with BCG, Infact Immun, 7 : 631, 1973.

27. Bornstein RS, Mastrangelo MJ, Sulit H et al : Immunotherapy of melanoma with Intralesional BCG, Natl Cancer Inst Monogr, 39 : 213, 1973.

28. Levy NL : Letter to the editor, Int J Cancer, 11 : 497, 1973.

29. Heise ER, Weiser RS : Factors in delayed sensitivity : Lymphocyte and macrophage cytotoxins in the tuberculin reaction, J Immunol 103 : 570, 1969.

30. Alexander P : Activated macrophages and the antitumor action of BCG, Natl Cancer Inst Monogr, 39 : 127, 1973.

31. Fauve RM : Antiinflammatory effects of murine malignant cells, Proc Nat Acad Sci, 71 : 4052, 1974.

32. Aungst CW, Sokal JE, Jager BV : Complications of BCG vaccination, Proc A mer Assoc Cancer Res, 14 : 108, 1973.

33. Mansell PWA, Kermentz ET : Reactions to BCG, JAMA 226 : 1570, 1973.

34. Sparks FC : BCG in cancer treatment, New Engl J Med, 290 : 343, 1973.