DOI: http://dx.doi.org/10.5915/15-1-12348

IMMUNOTHERAPY IN CHRONIC LYMPHOCYTIC LEUKEMIA

BCG Induced Long Term Remission

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SYNOPSIS-ABSTRACT

A case of chronic lymphocytic leukemia (C.L.L.) was treated with repeated administration of tumor dose Bacillus Calmette-Guerin *(BCG). Following the first immunization series, the case has gone into complete remission and has remained so up to the time of this report, for about 9 years. The leukemic lymphocytes appeared to be "null" cell type.*

Although major advances have been made in our understanding of the pathophysiology of chronic lymphocytic leukemias (C.L.L.) during the past two decades, the treatment of these leukemias has not changed significantly to improve the survival rate and the morbidity.[1] Median survival in most series is about 5 years.[1] BCG was introduced in the treatment of acute lymphocytic leukemias in the late 1960's. There has not been any published reports of BCG trials in C.L.L. In the present paper a case of C.L.L. treated with repeated BCG vaccination was reported. The first BCG vaccine appeared to produce a striking remission which was maintained by successive BCG administrations since 1973. The case at present seems to enjoy complete clinical and laboratory remission which is in its 9th year. Furthermore, the patient has experienced no detectable side effects from BCG treatment.

Report of a Case

The case is a 60 year old white male who was hospitalized in 1971 with the chief complaint of low back pain. In the routine lab profile, his white blood cell (WBC) count was noted to be in the 20 thousand range with 80% lymphocytes. Further studies including bone marrow biospy established the diagnosis of C.L.L. His physician elected to observe the course of the case without any specific treatment. For the ensuing two years the patient remained asymptomatic, and his WBC count stayed in the 20,000 range with normal hemoglobin (Hb) levels. However, by 1973 the WBC rose to the 50,000 count range with lowered Hb of 12.0 gm, and the patient was suffering from recurrent bacterial and viral infections. He was therefore referred to a hematologist for initiation of his leukemia therapy. His physical exam findings were as follows: spleen was palpable 1 cm down for the liver 2 cm down on the anterior axillary lines. Peripheral lymph nodes were readily palpable in the neck in the supraclavicular, axillary, and inguinal regions. In addition the patient complained of paresthesias involving the hands and feet, but there were no definite signs of peripheral neuropathy.

His family history might also be of interest in that his father died of C.L.L. at the age of 42 and his mother of "internal cancer" at the age of 51.

The patient was given a choice between conventional leukemia chemotherapy and BCG type immunotherapy. He elected the latter and received the first tumor-dose of BCG in April 1973: Glaxo culture Danish substrain BCG in the amount of 1 cc was administered intracutaneously by multiple (10-15 times) punctures on the lateral aspect of the thigh following 5 cc 2% Xylocain subcutaneous anesthesia. This was repeated in November 1974, June 1975, and April 1976. His pre-treatment Mantoux test which was negative turned positive 2 months after the first BCG, and remained strongly positive thereafter as tested at least once a year. In addition the patient received influenza vaccines every Fall since 1973 as recommended for susceptible individuals by U.S. Public Health.

Most pertinent lab and clinical findings during the course of treatment may be summarized as follows: within 3 months after the initial BCG vaccine the WBC count declined gradually from the 50,000 range to 18,000, leveling off between 23-28,000 thereafter. The patient has normal levels of IgG and IgA but "trace" quantity of IgM as determined in immunoelectrophoresis before BCG therapy started. Following BCG, IgM levels returned to normal. The lymphocytes appeared to have no surface markers of B or T cells, and therefore they were classified as "null" cells. In November 1976 further studies including those with blastogenetic agents were carried out: about 70% of lymphocytes were stimulated by phytohemag-

glutinins, 36% by Concanavalin-A (Con-A), and 11% by pokeweed antigens. The active T-cells were 7% which may be considered near normal levels in terms of absolute numbers (Normal 15-35%). There were **no** detectable B-cells. Serum complement levels were within normal limits.

The levels of Hb and platelets remained within normal limits (14.4-17.0 gm and 220-280,000) throughout the course. Recurring infections were no longer a problem. In fact the patient has been free of northern climate "colds" since 1973. His spleen, liver and lymph nodes were **no** longer palpable after 3 months of the first BCG and have remained so up to the time of this report. Another interesting lab finding was the presence of type IV hyperlipoproteinemia before immunotherapy. This returned to within normal limits after immunotherapy.

There appeared to be no serious side effects of BCG immunotherapy other than local abscess formation at the site of BCG. This was readily controlled by oral penicillin and local wound care.

Discussion

In view of such a striking response to BCG in this case, one may certainly raise several important questions. Was the favorable response to BCG due to "null" cells or because the case was at an early stage of C.L.L.? (Though this case may fall in stages 2-3 by the Rai et al. staging.)[2] Or was it related to the administration schedule of BCG, dosage, or mode of injections, etc.? Since there are **no** other reported cases of C.L.L. treated with BCG it is difficult to answer the above questions. Nevertheless perhaps it is worth re-emphasizing the positive changes which took place following the immunotherapy: In the laboratory profile Hb and WBC levels improved. The IgM and active T-cell levels returned to normal which correlated clinically that the case no longer suffered from bacterial and viral infections. Type IV hyperlipoproteinemia which improved after immunotherapy might have been due to the infections since some viral and bacterial agents could cause this type of laboratory abnormality.[3,4]

It has been well established in the literature that most C.L.L. cases have been B-cell type and the minority T-cell type.[1,5] Though the case reported here showed "null" cell typing, its blastogenesis indicated far more T-cell type characteristics as most of the cells appeared to be stimulated by phytohemagglutinins and Con-A. From the standpoint of prognosis and therapeutic response, there appears to be no real difference between T-cell and B-cell C.L.L.[1]

BCG immunotherapy in this case appeared to be side-effect free except for local abscess formation at the site of injections. Because C.L.L. cases are immunologically deficient in combating infections and BCG is known to produce low grade tuberculosis especially in the lungs and liver,[6] one should monitor this type of therapy accordingly.

Since no form of conventional therapy has unequivocally been shown to alter the prognosis of C.L.L.,[1] BCG immunotherapy may be included in our treatment armamentarium. Such therapy may further be justified through the latest work on the role of T lymphocyte subsets controlling B lymphocyte differentiation in C.L.L.[7] The following suggestions might be appropriate relative to the use of immunotherapy:

Start immunotherapy at the early stages of the disease preferably at stage 1 or 2 on the Rai et al. staging.[2]

Study in detail the immune status of the patient. Particular attention should be directed to the B and T cells, their subsets, and their terminal functional products. Such an "immune profile" should be monitored throughout the course of therapy. The immune profile is to be used as a guide to determine the timing of BCG administration, i.e., tailor-made protocol for each patient instead of using one protocol for all patients. This will furthermore prevent BCG "antigens-in-excess" produced immune paralysis which might promote tumor growth. Of course one should carefully monitor the side effects of BCG such as those of low grade miliary Tb, active granulomas in the lungs, liver, bone marrow and "BCG arthritis," etc.

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Acknowledgements: Merle S. Mark, M.D. of Crystal, MN referred the case. Clarence Everhart, M.D., pathologist at Golden Valley Health Center, Golden Valley, MN, reviewed the pathology slides.

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