Asian Pacific Journal of Allergy and Immunology (1986) 4 : 139-148

Immunologic Tools to Decipher Efficacy of BCG Immunotherapy in Advanced Breast Cancer : A One Year Follow Up Study

Kunal Saha,* Harish Kapila, Rajan Madan and R.N. Shinghal

SUMMARY **We report the clinical outcome of conventional therapy and BCG immunisation therapy for 40 patients with advanced breast carcinoma. The clinical outcome was better for the 20 patients receiving BCG immunisation therapy. All patients were assessed for cell mediated immunologic competence before starting treatment and after completion of treatment. Thereafter they were followed for one year. Those patients who showed good local response to BCG vaccination before starting therapy had better prognosis, and those for whom anergy to PPD and DNCB could be reversed by BCG immunotherapy showed clinical improvement. Another interesting finding was that IgA was the predominating immunoglobulin located in normal breast tissue and benign breast tumours while IgG was deposited in most of the malignant breast tumour. This indicated that malignant tumours of the breast jeopardise the secretory immune system of the mammary gland.**

Carcinoma of the breast ranks first among malignancies in Indian women. Its incidence is 20.40 per 100,000 population. Many Indian women are still illiterate, and thus, large number of them come to hospitals with advanced forms of the disease and with severely compromised immune systems. Furthermore, all the currently available modes of conventional treatment, including surgery and chemotherapy, have immunosuppressive effects. These probably jeopardise immunologic regulation mechanisms, impair immunologic surveillance and prevent immune killing of tumour cells.

In recent years, BCG immunotherapy of solid tumours has been attempted by several investigators.[1-3] Despite considerable activity in this field, we felt that more clinical trials were necessary in India to establish the usefulness of adjuvant therapy in patients with advanced breast cancer. Very recently, we completed a follow up study in patients with advanced breast carcinoma receiving chemo-immunotherapy using levamisole as the immune adjuvant; it showed encouraging results.[4] In this communication we present the results of treating 40 patients with advanced breast cancer using conventional therapy only (20 patients) or conventional therapy supplemented with BCG immunotherapy (20 patients). The groups were compared clinically for one year.

MATERIALS AND METHODS

Human materials and treatment schedules

Forty patients with stages III and IV (Manchester classification) breast carcinoma and ranging from 30 to 70 years of age were included in the study. They were divided into 2 groups. In group I (control) there were 11 patients with stage III and 9 patients with stage IV illness. Group II (experimental) had the same composition. Patients with stage IV illness had secondary metastasis in the lung (one patient), in the supraclavicular lymph nodes (4 cases), in the opposite breast (1 case), in the liver (2 cases), in the pericardium (1 case), in the local breast tissue (1 patient), in the same axilla (12), and in the opposite axilla (8 cases), in the skull (1 case), and in the pleura

From the Department of Bacteriology, Govind Ballabh Pant Hospital and the Department of Surgery, Maulana Azad Medical College, New Delhi-110002, India.

★ Present address : Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110007, India.

(effusion in 1 case). Table 1 shows the treatment schedule given to patients of both groups.

BCG immunotherapy

Every week for 8 weeks, 6×10^8 viable units of BCG was applied over an area of 5 cm^2 on the anterior aspects of the forearm or thigh. Pressure was exerted to break through the epidermis. The area was covered with BCG suspension. The arm or thigh was covered with a cardboard shield and the reaction was read after 5 days.

The reactions to BCG immunisation were classified as follows : (a) Type I BCG reaction = No visible response or slight oedema (indicator of anergy) ; (b) Type II BCG reaction = Patchy mild erythema and oedema along with scarification line and mild systemic symptoms like fever and arthralgia ; (c) Type III BCG reaction = The optimal response, with confluent erythema and oedema where erythema might exceed the limits of scarification by up to 1 cm, where flaring of previous scarification might occur and where regional lymph nodes might be painful and tender ; (d) Type IV BCG reaction = Very severe local reaction and systemic symptoms.

Clinical assessments

The clinical assessments of the response to therapy were performed according to Hayward *et al.*[5] Thus, disappearance of all lesions was taken as complete remission ; 50% decrease in existing lesions was taken as a partial response ; less than 50% decrease in existing lesions or less than 25% increase in existing lesions was taken as no response ; appearance of new lesions or 25% increase in existing lesions was taken as progressive illness. Other lesions such as pleural effusion were examined by chest x ray. Bony metastasis was assessed by scanning.

Immunological assessments

(i) **The delayed hypersensitivity reaction** (DHR) against graded doses of tuberculin (1, 10 and 100 TU) was studied and DHR against dinitrochlorobenzene (DNCB) was performed.[2]

(ii) **Estimation of peripheral blood T lymphocytes** was performed using the SRBC rosette technique.[2]

(iii) **Peripheral blood B lymphocytes** were estimated using FITC antihuman immunoglobulin (Kallestad Laboratories, U.S.A.).

The percentage of B lymphocytes was taken as the percentage of the total viable lymphocytes bearing immunoglobulin. Absolute B cell counts were calculated from the total lymphocyte counts and the percentage of B cells. All tests were repeated after a period of 2 months. During this period, immunostimulation was given in the BCG group only.

(iv) **Immunoglobulin deposits in breast tumours** Biopsies were taken from 6 of the control group patients, and included tissues from one normal breast, 3 dysplastic breasts, one fibroadenoma breast and one chronic abcess breast. Biopsies from 13 malignant tumours (8 primary and 5

Table 1 Treatment administered in the patients with breast carcinoma

Conventional treatment	Number of patients	
	Group I (20)	Group II (20)
Surgery	16	15
Radiotherapy	12	10
Hormone therapy	3	3
Chemotherapy*	5	4
No treatment	none	2

Group I consisted of control patients. They were given conventional treatment only. Group II consisted of test cases, who received BCG in addition to the conventional treatment. No gap was given between conventional therapy and immunotherapy. The most usual treatment instituted for stage III illness was simple mastectomy with radiotherapy and if needed, hormone therapy ; whereas for stage IV illness toilet mastectomy, chemotherapy and hormone therapy were given. Radiotherapy was given in lung metastasis.[4]

*Cyclophophamide was given in the dose of 500 mg intravenously on the first and eighth days ; 10 mg methotrexate was administered on the second, fifth, tenth and thirteenth days ; 500 mg 5-fluorouracil was given intravenously on the third and eleventh day. Steroid was given in combination. The cycle was repeated every 28 days (Saha *et al*, 1985). Total and differential leucocyte counts and haemoglobin levels of the patients were estimated. Platelets were counted once in every cycle. If the leucocyte counts fell below 4000/mm^3, but were about 3000/mm^3, the dose of chemotherapy was reduced by 50%. However, if the counts fell below 3000/mm^3, chemotherapy was withheld until leucocyte counts rose to about 4000/mm^3. Whenever chemotherapy was withdrawn due to myelosuppression, immunotherapy was not discontinued.

metastatic) were included. Deposits of immunoglobulin G, A and M in the above breast tissues were studied by the direct immunofluorescent technique using FITC-antihuman IgG, IgA and IgM antiserum (Meloy Laboratories, U.S.A.). The method has been described elsewhere.[6]

Clinical course of the disease

All patients were followed up clinically for one year.

RESULTS

Improvement of cell mediated immunity following BCG immunotherapy

The immune responses were markedly depressed in all patients with stage III and IV breast cancer. Before starting any form of treatment, only 5 (12.5%) and 17 (42.5%) patients out of the 40 belonging to both groups responded to PPD and DNCB, respectively (Table 2). In contrast, 100% of non-cancer individuals responded to DNCB.[7] After BCG immunostimulation was given to 20 group II patients, 55% responded to PPD and DNCB. In contrast, only 20% and 40% of the patients in group I were able to respond to PPD and DNCB, respectively, following conventional therapy (Table 2). Thus a definite improvement of DHR was noticed in some patients who received conventional treatment along with BCG immunostimulation. In contrast, the immunologic status of some group I patients deteriorated after completion of the treatment schedule (Table 2). This indicated that chemotherapy, radiotherapy and/or surgical treatments perhaps made these patients immunodeficient.

Table 3 shows that the mean absolute T cell counts increased by only 5% following conventional therapy ; however, after combination therapy, it increased by 15%. The mean B cell percentage, on the other hand, decreased from 28.0 ± 2.4 (24-32) to 21.0 ± 1.9 (18-24) in group I patients but it remained unchanged in group II patients. At the start, the mean value was 28.7 ± 2.7 (23-35) and after the end of the treatment schedule, it was 29.4 ± 2.4 (25-33). McCluskey and associates showed that the total number of blood T-cells remained unaltered in breast cancer patients. However the T-helper to T-suppressor cell ratio decreased below 1.0 in stage IV illness.[8]

Table 2 Stimulation of immunologic responses in anergic patients with stage III and IV breast carcinoma by BCG

Group (n)	Positive PPD response n (%)		Positive DNCB response n (%)	
	Before starting conventional or combination therapy	Two months later*	Before starting conventional or combination therapy	Two months later*
Group I : Conventional therapy (20)	5 (25)	4 (20)	10 (50)	8 (40)
Group II : Combination therapy (20)	None	11 (55)	7 (35)	11 (55)
Chi-square (Responder after treatment)		26.20		11.55

*Two months after starting conventional treatment and BCG immunotherapy, the tests were repeated. A definite improvement of delayed hypersensitivity reaction was noticed in more patients who received combination therapy in comparison to those who received only conventional treatment. However, Chi-square analysis between the responders of both groups after undergoing conventional and combination therapies showed no significant difference.

Course of the disease following combination therapy and its relation to immunologic assessments

Table 4 shows that only 2 group II patients and 6 group I patients died during the study period. The mortality rate for patients with stage III illness was less than that for patients with stage IV disease. Thus within group I patients, 2 out of 11 (18%) patients with stage III illness died within one year, whereas 4 out of 9 patients (44%) in the same group with stage IV illness succumbed within the same time. In group II patients, on the other hand, 1 out of 11 (9%) cases with stage III and 1 out of 9 (11%) cases with stage IV illness died within the one-year follow up period. Also, the number of patients with progressive forms of illness was less in the second group than in the first. Furthermore, complete remission was observed in only one patient belonging to group II. These results perhaps suggest that combination therapy if given before the development of stage IV disease may reduce the mortality in the patients. However, more data are necessary for any definite conclusion.

Table 5 shows that the functional immunity of the patients with advanced breast carcinoma could be greatly potentiated by non-specific immunostimulation with BCG, thereby retarding the progress of their disease. Thus, while the PPD and DNCB status improved in none of the group I patients, 11 group II cases became PPD responsive and their illness remained stationary. Also, seven patients in the same group showed DNCB conversion, and their disease was arrested. Further analysis showed that 4 cases from group II showed both PPD and DNCB conversion following combination therapy. Their illness became stationary. Only 3 patients of group I showed a rise in T cell counts after conventional therapy ; for two of them, the illness was arrested. On the other hand, 6 cases in group II showed increased T cell counts after combination therapy ; one had complete remission of illness and 5 showed arrested disease. At the same time, 9 cases in group I showed decreased T cell counts after conventional therapy. They derived no benefit from treatment. Only 4 group II patients had decreased T cell counts. They showed no response after combination therapy.

We have taken complete remission and stationary illness as indications of beneficial effects of treatment. In group II, the course of the illness becames stationary in 8 (40%) patients and one patient (5%) showed complete remission. In contrast, the disease remained stationary in only 3 (15%) group I patients following conventional therapy. None in this group showed complete remission of the disease. Thus, our study has

Table 3 Immunostimulation of patients with breast cancer by combination therapy and its effect on peripheral blood lymphocyte counts and absolute T cell counts

Group (n)	Absolute lymphocyte count in millions/ml (Mean ± SD (range)		Absolute T lymphocyte count in millions/ml (Mean ± SD (range)	
	Before starting conventional treatment or combination therapy	Two months thereafter	Before starting conventional therapy	Two months thereafter
Group I : Conventional therapy (20)	2.769 ± 0.414 (2.240–3.440)	2.842 ± 0.392 (1.980–3.440)	1.134 ± 0.237 (0.784–1.417)	1.193 ± 0.265 (0.653–1.651)
	t value = 0.54		t value = 0.54	
Group II : Conventional therapy and BCG (20)	2.503 ± 0.684 (1.340–3.668)	2.397 ± 0.601 (1.620–3.976)	0.943 ± 0.288 (0.428–1.508)	1.095 ± 0.405 (0.491–2.067)
	t value = 0.37		t value = 1.01	

The mean absolute counts of peripheral blood lymphocytes in normal subjects was 2.560 ± 0.730 millions/ml. The T-lymphocyte percentage in healthy subjects was 55.5 ± 6.57 Statistical analysis showed no significant change in the total blood lymphocyte and absolute T cell counts in the patients belonging to both groups.

Table 4 A comparative study of the clinical courses of the patients with advanced breast cancer following conventional and combination treatments (A one year follow up study)

	Improvement			Deterioration	
	Regression or Stationary		Partial remission	Progressive	
				Progressive or no response	Progressive and death
Group I : Conventional therapy (20)	None	6 cases	6 cases	8 cases	6 cases
Group II : Conventional treatment and BCG (20)	1 case	8 cases	5 cases	6 cases	2 cases

In one combination therapy case, regression of disease was observed. Six cases receiving conventional therapy died within the course of one year, while only 2 cases receiving combination therapy died within the same time. Thus the mortalities were 30% and 10% in group I and group II, respectively. However, Chi-square analysis showed that the difference was not statistically significant (Chi-square = 0.031).

Table 5 Immunologic improvement or deterioration in patients with advanced breast carcinoma following conventional or combination therapies and its relationship to the course and prognosis of the illness

Immunologic state of the patients following treatment	Types of treatment given	
Improved/Deteriorated	Group I : Conventional treatment (20 patients)	Group II : Combination therapy (20 patients)
PPD status : Improved/Deteriorated	None/1 case (PR)	11 (PR = 3 ; S = 7 ; CR = 1) /None
DNCB status : Improved/Deteriorated	None/1 case (P and died)	7 (**S = 7) /none
Both PPD and DNCB status : Improved/Deteriorated	None/None	4 (**S = 4) /None
Rise in T cell count/Fall in T cell count	3 cases (S = 2 ; **P = 1) / 9 cases (NR = 2 ; PR = 6 ; P and died = 1)	6 cases (CR = 1) /4 (PR = 1 ; NR = 3 ; **S = 5)
Patients responsive to PPD and DNCB before starting treatment and remained responsive to both the tests following treatment and also showed rise of T cell count after completion of therapy/ Patients unresponsive to both the tests along and showed fall of T cell count following completion of treatment	1 cases (S = 1) **/ 5* cases (P = 1 ; P and died = 1 ; PR = 2 ; NR = 1)	None/2 cases (NR = 2)

CR = complete remission ; PR = partial remission ; S = Stationary ; CR = complete remission ; NR = no response ; P = progressive
Stationary and complete remission were taken as signs of clinical improvement.
*One had pulmonary tuberculosis and another had metastasis in the lung.
**More patients showed clinical benefit in group II.

suggested that combination therapy is perhaps more beneficial than conventional treatment in improving the immunologic status and retarding the downhill course of advanced breast cancer. However, more trials are necessary for any definite conclusion.

Reactions of BCG immunotherapy and prognosis

BCG was poorly tolerated by our patients. All had complications including ulceration at the injection site such that a reduced dosage of one half was required for 2 patients. None had disseminated BCG disease or hepatic dysfunction. Other minor complications were fever (18 cases), anthralgia (13 cases), transient proximal lymphadenopathy (9 cases) and erythema with itching at local sites (16 cases). BCG did not enhance or reduce myelotoxicity of chemotherapeutic drugs used in our patients.

Severity of BCG reaction was studied in only 10 out of 20 patients. It is interesting that ulcers healed well in patients who responded to therapy and achieved remission but poorly in patients with progressive disease. Table 6 shows that the severity of BCG response observed in our patients could be used to predict the course of their illness.

The impairment of DHR observed in advanced breast cancer was remarkable. Thus, only 11 out of 22 cases (50%) with stage III illness and only 6 out of 18 patients (33%) with stage IV disease could respond to the hapten (Table 7). This was further demonstrated by the severity of reaction to BCG (Table 6). Patients with stage IV illness showed a poor response to BCG vaccination. They remained anergic to PPD and DNCB even after BCG immunotherapy and they showed a poor increase in T cell count after immune stimulation. On the other hand, patients with stage III illness showed satisfactory PPD and DNCB conversion, a 13% rise in T cell count and a grade III reaction to BCG. These immunologic findings could be correlated with the course of the disease (Table 6).

Cancer and the secretory immune system of the breast

Table 8 shows the classes of immunoglobulin deposited within the benign and malignant tumours of patients in this study. IgA and IgM deposits were predominantly found in normal and benign

Table 6 Severity of BCG reaction studied on the 5th day after immunisation and its relationship to immunologic status of the patients and to disease course

Severity of BCG reaction (Grade)	Number of cases 10	Absolute T cell count/mm^3		State of illness	Course of illness	Immunological status	
		At start	After completion of therapy (% T cell rise)			At start	After completion of therapy
I	1	695	792 (14%)	IV	Progressive (1 case)	PPD$^-$ DNCB$^-$	– –
	1 Associated pulmonary tuberculosis	784	824 (5%)	IV	Progressive (1 case)	DNCB$^-$PPD$^-$ DNCB$^-$	– –
II	2	539	588 (9%)	IV	Progressive (1 case)	PPD$^-$ DNCB$^-$	– –
		1006	1170 (6%)		Stationary (1 case)	PPD$^-$ DNCB$^-$	+ +
III	6	772*	879* (13%)	III	Stationary (6 cases)	PPD$^-$(6 cases) DNCB$^+$(3 cases)	+ (6 cases) + (6 cases)
IV	None	–	–	None	None	–	–

This table shows that very advanced stages of cancer, progressive illness, immunologic anergy to PPD and DNCB before and after BCG challenge, low initial T-cell along with low response of T cell count following BCG immunotherapy were all related with type I and type II BCG reactions ; on the other hand, type III BCG reaction was often seen in patients with less advanced disease, who showed some delayed hypersensitive response and a rise in absolute T cell count following BCG therapy and clinical benefit.

* Mean T cell count.

Table 7 Stimulation of dinitrochlorobenzene response in patients with breast carcinoma by combination therapy and its relation with stages of breast carcinoma

Group (n)	Stage of disease (n)	DNCB responsiveness in number (%) of patients	
		Before starting conventional treatment or combination therapy	After completion of conventional therapy with or without immuno-stimulation by BCG
Group I : Conventional therapy (20)	III (11)	7 (63)**	6 (54)** (a)
	IV (9)	3 (33) **	2 (22)** (b)
Group II : Combination therapy (20)	III (11)	4 (36) *	7 (63)* (c)
	IV (9)	3 (33) *	4 (44)* (d)

*There was a definite improvement of DNCB responsiveness in some patients who received combination therapy. This is more evident in the patients with stage III illness.

**There is deterioration of DTH reaction in some group I patients. However, there was no statistically significant difference of DNCB responsiveness shown by stage III or stage IV patients following conventional therapy or combination therapy.
Chi-square between (a) and (c) = 0.185;
Chi-square between (b) and (d) = 1.00.

Table 8 Classes of immunoglobulins deposited within malignant of breast tumours from patients treated with combination therapy and relationship of these deposits with the course of illness and prognosis. Only 13 samples were processed before starting BCG immunisation

Group (n)	Direct fluorescent antibody technique showing immunoglobulin deposits in mammary glands (number of samples and their percentages)						
	IgA	IgM	IgG	IgA & IgM	IgG & IgM	IgG, IgM & IgA	None
(A) Control mammary gland* (6)	5 (81%)	4 (67%)	1 (16%)	4 (64%)	0	1 (16%)	1 (16%)
Type of tissue							
(a) Normal (1)	1	1		1			
(b) Dysplasia (3)	3	3	1	3		1	
(c) Fibroadenoma (1)	1		1				
(d) Chronic breast abscess (1)							1
(B) Infiltrated duct carcinoma (13)	1 (18%)	3 (24%)	7 (56%)	0	3 (24%)	0	5 (40%)
Type of tumour							
(a) Primary cancer (8) course of illness	1 (PR = 1)	2 (PR = 2)	4 (S=1; P=2; PR = 1)	0	2 (P = 2)	0	4 (PR=3; P=1)
(b) Metastatic (5) cancer course of illness	0	1 (CR =1)	3 (D=2; P = 1)	0	1 (D= 1)	0	1 (P =1)

*Controls included biopsies from one normal breast, one chronic abscess, one fibroadenoma and 3 mammary dysplasia. All benign diseases cured after surgery. IgA and IgM were detected more frequently in control breast tissues and benign tumours, while IgG was more frequently detected in malignant tumours. Also no immunoglobulin was detected in 4% malignant tissue. Deposits of IgG in malignant breast tumours and absence of any immunoglobulin were associated with bad prognosis.

CR = Complete remission ; S = Stationary ; PR = Partial remission ; P = Progressive disease ; D = Progressive and died.

tumours. On the other hand, IgG deposits were predominant in malignant tumours. Also, 5 out of 13 malignant tumours showed no immunoglobulin deposits. Thus, 12 out of 13 malignant patients studied had either IgG deposits or no deposits. Of these 12 patients, 2 died, 5 had progressive disease, 4 showed partial remission and only one was stationary indicating an association with bad clinical course (Figs. 1 and 2).

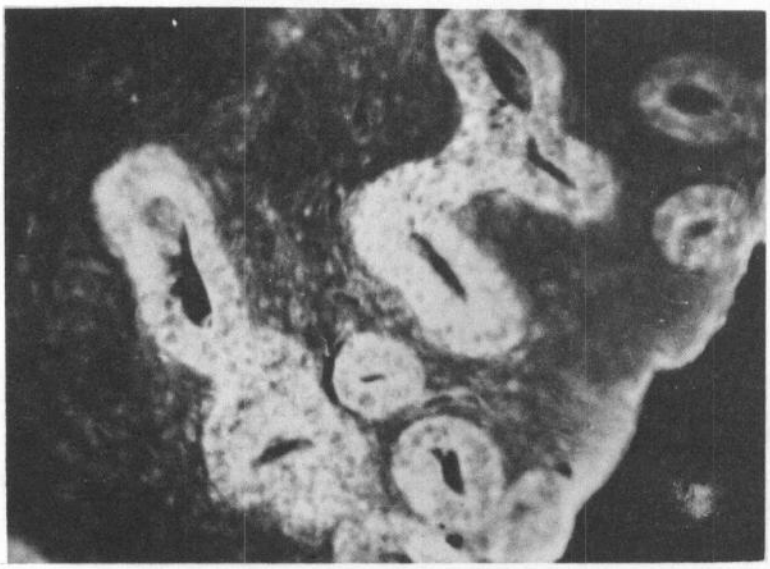

Fig. 1 Immunoglobulin G localisation in mammary dysplasia.

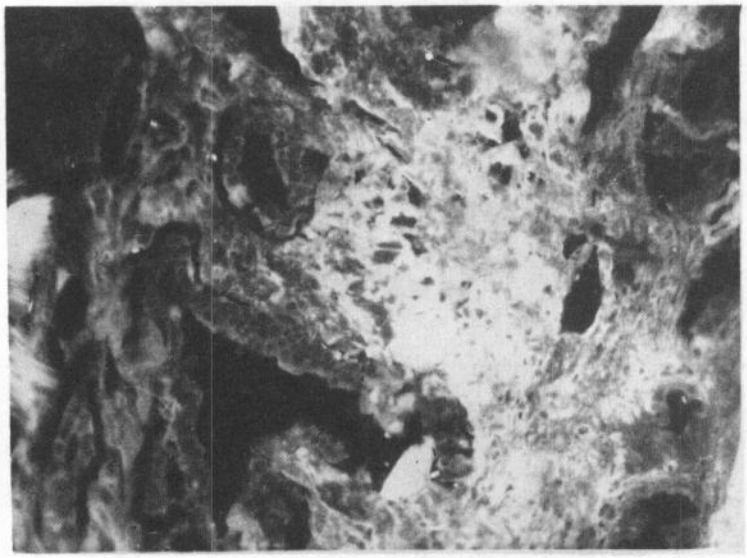

Fig. 2 Immunoglobulin G localisation in a primary infiltrating duct carcinoma of the left breast (Stage IV) in a 38 years old female (premenopause). After undergoing Patey's mastectomy, she had local recurrence, developed nodular auxiliary lymphadenopathy and enlarged hard liver. She was treated with cyclophosphamide, methotrexate and 5-fluorouracil. Epithelial cells of the tumour and undifferentiated areas showed IgG deposits.

DISCUSSION

BCG Immunotherapy in advanced breast cancer and its comparison with levamisole

It was shown in an earlier study that levamisole could potentiate the cellular immune response in stage III and IV breast carcinoma patients whose CMI was severely compromised by tumour load.[4] The improvement of immunity in these patients was possible only after reduction of tumour load either by surgery or by chemo-and/or radiotherapy. Once the tumour burden was removed, combination therapy proved more effective than conventional treatment in retarding the progress of illness.

Among the methods employed for non-specific augmentation of immune reactivity with adjuvants, BCG, *C. parvum*, levamisole, lentinan, interferon and its inducers are mostly used. The reticulo-endothelial system, which is associated with prevention of tumour growth, can be potentiated by BCG. It exerts a non-specific cytostatic effect on human tumour cells *in vitro*.[9] Macrophages, activated by BCG, facilitate the processing and presentation of tumour antigens to immunologically competent lymphocytes within the tumour or in the regional lymph nodes. Hortobagyi *et al*[10] have shown superior results for chemo-immunotherapy with BCG and levamisole than without.

The effectiveness of BCG immunotherapy for solid tumours is variable. Optimal tumour size is critical. Table 4 shows that in 9 out of 20 BCG immunotherapy cases here, the illness either regressed or became stationary. This is similar to the observations in an earlier

study where 8 out of 20 cases treated with levamisole showed either regression or arrest of illness.[4] Besides tumour size, other important factors for clinical improvement are the ability of the patient to develop an immune response to tumour antigens, the injection of adequate numbers of viable BCG organisms and the proximity of the BCG to the tumour cells.[1]

In the present study, immunotherapy with BCG converted more PPD unresponsive patients (Table 2) than did levamisole in our earlier study.[4] However, the DNCB conversion rate was similar in both treatment schedules. The mean absolute T-cell count rose only 5.5% for our patients receiving combination therapy plus BCG immunization. Six out of 20 cases showed an increase, while 9 showed a decrease (Table 3). In contrast, combination therapy with levamisole gave a 26% increase in T cell count (12 out of 20 patients showed increased T cell counts, while none showed a decrease).[4] This difference might be due to the fact that BCG has been found to induce also suppressor T cells.[11]

BCG is a polyclonal B-cell activator.[1] It enhances antibody formation through the induction of T-helper cells.[12] Our patients receiving BCG immunotherapy showed a 15% rise in B cell count. On the other hand, conventional therapy gave only a 5% rise. Earlier, we showed that B-cell counts did not change in breast carcinoma patients who received conventional therapy plus levamisole immunostimulation.[4] Olusi and associates demonstrated that levamisole restored spontaneous rosette-forming lymphocytes, delayed cutaneous hypersensitivity reactions and reconstituted the histological integrity of the thymus in malnourished rats.[13] It had no effect on plaque-forming cells. In contrast, large doses of BCG induce antibody and inhibit DTH. This DTH blocking effect has been suggested to arise from antigen-antibody complexes which accumulate in the serum of heavily immunised patients.[14] The impairment of cellular immunity, as evident by the fall in T cell count, might be responsible for the progressive illness in 6 of the 20 patients receiving BCG immunisation (Tables 4 and 5).

There are certain risks with BCG administration.[9] Intratumoral injection of BCG is more hazardous than the scarification technique, which is well tolerated. We found no instance of anaphylactic reaction, disseminated infection or hepatic dysfunction.

Immunological tools to decipher the functions of the immune system

The impairment of DHR observed in our advanced breast cancer patients was remarkable (Table 7). This is further substantiated by the poor BCG reactivity shown by stage IV patients (Table 6). The severity of BCG reactivity in our patients was associated with the rise of T cell count, DHR positivity and improved clinical course.

Secretory system of the breast, its alteration in malignancy and prognosis

The relationship between the breast and the immune system is of interest in the study of breast neoplasia. As a part of the secretory immune system, the breast is a site for the synthesis and secretion of IgA. Indeed, immunoglobulin A is the most abundant immunoglobulin of human breast milk. IgM is also synthesised and secreted by the normal breast at a lower concentration than IgA.[15] In our study, IgA was the most common (80%) immunoglobulin located in normal breasts and in benign breast tumours (Table 8). IgM was positive in 67% of benign breast lesions. The presence and production of IgA and IgM in the normal breast contrasted with the altered or lost ability to secrete these immunoglobulins in cancerous breast epithelium (Table 8).

The immune system pattern in neoplasia thus appeared to differ from that for non-neoplastic lesions of the breast. Using indirect immunofluorescence, Richman observed that IgA and IgM were frequently associated with benign tissues, while IgG was not.[16] In our tests, IgG was positive in 5% of the primary breast cancer cases and in 60% of the metastatic breast cancer cases (Table 8). McCarty and coworkers reported localisation of IgG in 35.3% of primary breast cancer cases and 48.5% of metastatic breast cancer cases.[17] They found IgG localisation significantly more often among estrogen-receptor-negative tumours. Although we did not carry out hormone studies, we observed that 7 out of 13 samples showed IgG deposits and 5 samples showed no immunoglobulin. From the relevant patients, all except one developed progressive illness and none responded to BCG immunotherapy. Thus, a study of immunoglobulin localisation in breast tumours can be helpful in predicting how the immune system will function and how it will direct the course of disease. The most accepted prognostic factors are the number of positive lymph nodes, the estrogen receptor content and the menopausal status.[18]

Our results based on a one-year follow-up study have shown that

(i) BCG immunisation in breast cancer patients has immunopotentiating action. It has some

clinical benefit in progressive illness and can slow the progress of the disease ;

(ii) The cellular immune response shown by patients at the site of BCG vaccination is associated with the clinical outcome of BCG immunotherapy ;

(iii) The immunologic secretory system of the human breast is jeopardised in malignant breast tumours. Normal breast tissues show IgA and IgM. Localisation of IgG as well as disappearance of all immunoglobulins from the tumour tissue are bad prognostic signs.

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