Cancer Immunol Immunother (1982) 13: 174–175

Cancer Immunology Immunotherapy

Regional Immunotherapy in Resectable Squamous Cell Lung Carcinoma

Analysis of a Randomized Study

N. Roeslin[1], J. M. Lang[2], G. Morand[1], J. M. Wihlm[1], and J. P. Witz[1]

[1] Service de Chirugie Thoracique Hôpital Civil, F-67091 Strasbourg Cedex
[2] Service des Maladies du Sang, Hôpital Hautepierre, F-67091 Strasbourg, France

Summary. *Patients with resectable squamous cell carcinoma were randomly allocated after surgery to receive either no further treatment (57 patients) or a single intrapleural injection of BCG (61 patients). No significant improvement in survival was observed in patients treated with BCG, even when their disease was staged as N_0. These was a slight trend for the recurrence rate to be lower in patients classed as N_0, but this was not significant.*

Introduction

The local and regional immune system may be of major importance in antitumor defence to prevent tumor recurrence after surgery, as suggested for example by the encouraging results reported in patients with stage I lung cancer treated with intrapleural *bacillus Calmette-Guérin* (BCG) by McKneally et al. [3]. This paper reports an analysis of a prospective randomized trial to evaluate the possible benefit of combined surgery and adjuvant intrapleural BCG in resectable squamous lung carcinoma, a type of lung cancer whose growth may remain localized for longer than that of other forms of non-small cell carcinoma.

Patients and Methods

Only patients with histologically proven squamous cell carcinoma that was previously untreated and was considered fully resectable and potentially curable by surgery alone were eligible for the present study.

Between 1 January 1978 and 1 September 1980 118 patients were operated upon and staged according to a TNM classification adapted for resected tumors [4]; the patients were then randomized between two groups.

Group A (61 patients) received a single intrapleural injection of 1 ml lyophilized BCG obtained from the Pasteur Institute and containing 1.2×10^7 living units between days 5 and 7 post-surgery. BCG was either directly injected by thoracocentesis in the post-pneumonectomy cavity, or administered through a chest tube in the mediastinal position in patients subjected to lobectomy. Two weeks after BCG injection, isoniazid was given at a daily dose of 300 mg for 3 consecutive months. Except for the source of BCG, this protocol is identical with that used by McKneally et al. [3]. Group B was made up of 57 patients treated by surgery alone, without BCG or placebo injection. No additional therapy was administered to any patient in either group. The median follow-up duration for alive patients is 39 months (range, 15–48 months). Tables 1 and 2 show the distribution of the patients between the two study groups.

Survival was analysed by actuarial calculation: the survival rate was compared by a Gaussian distribution test. The recurrence rate in the two groups was compared using the χ^2 test.

Results

As shown in Tables 1 and 2, the two groups of patients were quite comparable except that the number of limited resections

Table 1. Destribution of clinical, radiological, pathological and operative data

	BCG group	Control group
n	61	57
Non-smoker	3	2
Smoker > 10 cigs./days	56	54
Periodic examination	28	25
Infection	15	15
Hemoptysis	13	9
Chest pain	5	8
Normal Rx	3	–
Coin lesion	39	35
Lobar opacity	18	22
Right lung	32	31
Left lung	29	26
T_1	23	25
T 2_1	24	17
T 2_2	2	1
T 2_3	12	14
N_0	42	35
N_1	11	16
N_2	8	6
Lobectomy	42	27
Bilobectomy	6	8
Pneumonectomy	13	22

Table 2. Distribution of the patiens between the two groups by conventional stages of lung cancer

Stage	BCG group	Control group
Stage I	45	42
Stage II	9	9
Stage III	7	6
N	61	57

Reprint requests should be addressed to N. Roeslin

0340-7004/82/0013/0174/$ 01.00

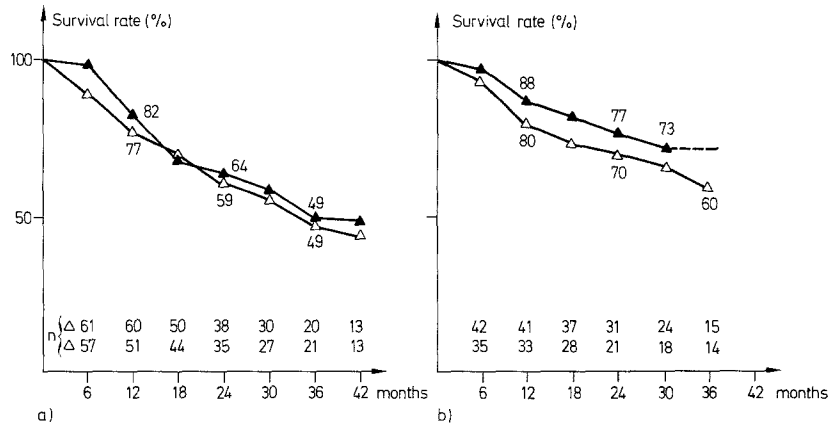

Fig. 1a and b. Post-surgery survival rates for all patients (**a**) and for N_0 patients (**b**) in control (△———△) and BCG (▲———▲) groups

(lobectomies) was higher in the BCG group, compared with pneumonectomies, than in the control group. Post-operative death due to pulmonary embolism, pulmonary infection, or bronchial fistula was observed in four patients: three in the control group and one in a patient treated with BCG. Three further patients died during follow-up for reasons not related to cancer or treatment. BCG injection induced high fever in 55/61 patients, lasting for 3 days in 40 patients and more than 3 days in 15. No other complications, either immediate or delayed, were noted that were attributable to BCG.

Actuarial analysis of survival was performed for all patients in each group (Fig. 1a) and for those without involved lymph nodes on examination of surgery specimens (stage IN_0 patients) (Fig. 1b). As shown in Fig. 1, we did not find any significant improvement in survival of patients receiving intrapleural BCG, even when staged N_0. Objective tumor recurrence was documented in 12/42 N_0 patients (28%) treated with BCG, and in 12/35 N_0 patients (34%) in the control group. When all patients (N_0, N_1, and N_2) in the two groups were considered the overall recurrence rate was 43% (26/61) in the BCG group, as against 42% (24/57) in controls. These differences are not statistically significant ($P < 0.4$; $P < 0.5$), but a slight trend to a reduced recurrence rate in N_0 patients was seen.

Discussion

Apart from a non-significant trend to reduced recurrence rate in patients staged N_0, we did not find any benefit of adjuvant therapy with intrapleural BCG, in this randomized trial. This is in accordance with data reported by others [1, 2, 5], and does not support the impressive results published by McKneally et al. [3]. The discrepancy may be due to the BCG strain used, patient selection, or too short a follow-up. The Pasteur Institute lyophilized BCG used in our trial contains at least as many viable organisms as the BCG. Tice strain used by McKneally et al., and is not considered less efficient as an immunotherapeutic agent. All patients who had positive lymph nodes removed together with the tumor were eligible for the present trial, as well as the N_0 patients in our series; none revealed any beneficial effect of intrapleural BCG. The slight differences in surgical procedures between the two groups would have made for more favorable results in the BCG group if anything.

The number of patients in our study is sufficient for statistical analysis. We conclude from these data that it is highly unlikely that intrapleural BCG was beneficial as administered in our protocol.

Acknowledgements. We acknowledge the technical and statistical assistance of Prof. M. Roos.

References

1. Jansen HM, The TH, Orie NGM (1980) Adjuvant immunotherapy with BCG in squamous cell bronchial carcinoma. Thorax 35: 781–787
2. Lowe J, Iles PB, Shore DF, Langmann MJS, Baldwin RW (1980) Intrapleural BCG in operable lung cancer. Lancet 1: 11–14
3. McKneally MF, Maver C, Kausel HW, Alley RD (1976) Regional immunotherapy with intrapleural BCG for lung cancer. J Thorac Cardiovasc Surg 72: 333–338
4. Renault P (1977) Valeur prognostique des structures. Le code T.N.M. Rev Fr Mal Respir 5 [Suppl 2]: 45–58
5. Wright PW, Hill LD, Peterson AV, Pinkham R, Johnson L, Ivey T, Bernstein I, Bagley C, Anderson R (1978) Preliminary results of combined surgery and adjuvant bacillus Calmette-Guérin plus levamisole treatment of resectable lung cancer. Cancer Treat Rep 62: 1671–1675

Received June 1, 1981/Accepted May 11, 1982