Intrapleural immunotherapy with Corynebacterium parvum in recurrent malignant pleural effusions

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ABSTRACT   Twenty-one patients with proven recurrent malignant pleural effusions were randomly allocated to treatment groups receiving either intrapleural *Corynebacterium parvum* in a dose of 7 mg or intrapleural mustine (20 mg). The designated intrapleural therapy was repeated on one occasion if further pleural aspiration was required. *Corynebacterium parvum* (nine patients) proved superior to mustine (12 patients) in suppressing the reaccumulation of pleural fluid, and was associated with only minimal side-effects of fever and nausea in two patients. Mustine caused marked nausea and vomiting in almost all patients. Three of the four patients who were deemed "failures" after mustine therapy had complete suppression of pleural fluid reaccumulation after a single dose of *C parvum*, the survival of the fourth being too short to assess a response adequately. There were no failures in the *C parvum* treated group. *Corynebacterium parvum* appears to be an effective, well-tolerated agent in the management of recurrent pleural effusions. The relative contribution of its potent immunological stimulant effect to its mode of action remains uncertain.

Successful suppression of the rapid reaccumulation of pleural fluid can make a major contribution to the management and palliative care of patients with disseminated cancer. Various methods of achieving this aim have been described, as recently summarised by Stiksa *et al*.[1] Chemical pleurodesis can be induced by intrapleural instillation of nitrogen mustard,[2] radioactive colloidal gold,[3] doxorubicin,[4] or quinacrine.[1] More invasive treatments have included iodised talc pleurodesis[5] and pleurectomy,[6] the latter requiring a limited thoracotomy. These invasive procedures are more successful than chemical pleurodesis which is successful in 50–70% of cases, but the simplicity of the technique of intrapleural injection of chemical agents after pleural aspiration has led to the continued use of such agents, and in particular intrapleural mustine, as a first line treatment of recurrent effusions.[7] Most patients experience nausea and frequently vomit after mustine treatment and in the search for a more effective, better tolerated, intrapleural therapy, the use of *Corynebacterium parvum* has been suggested. Webb *et al*[8] reported six patients with malignant peritoneal or pleural effusions who responded well to *C parvum*. In most patients complete suppression was

achieved, but only two of their patients had recurrent pleural effusions.

These promising results led us to compare intrapleural mustine therapy with intrapleural *C parvum* in a randomised group of patients with recurrent malignant pleural effusions.

Methods

Twenty-one patients with recurrent effusions associated with histologically proven malignant disease were entered into the study. All had required at least two pleural aspirations because of recurrent effusions and all had symptoms of dyspnoea, cough, or local pain. Sixteen of the patients had an underlying bronchogenic carcinoma while single patients had carcinoma of the breast, ovary, colon, bladder, and kidney. On entry to the study patients were allocated at random to one of two treatment groups. After complete aspiration of pleural fluid using an Abrams pleural biopsy needle, group A received an intrapleural instillation of mustine in a dose of 20 mg. This dose was repeated on one further occasion if repeat aspiration proved necessary. Group B received intrapleural instillation of *Corynebacterium parvum* in a dose of 7 mg (1 ml Coparvax Wellcome Foundation Ltd Lot BA 4031). A second dose of 7 mg was given if

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a further aspiration was required. Symptoms such as nausea, vomiting, and local pain related to the intrapleural therapy were recorded. The patients were followed carefully and reaccumulation of fluid monitored radiologically. Patients requiring no further aspirations and who experienced relief of symptoms were deemed successes, while patients requiring one further aspiration were considered to be a partial success, and repeated aspirations a failure.

Results

Of the 21 patients, 12 were treated initially with intrapleural mustine and nine received intrapleural *C parvum*. The details of these patients are listed in table 1. There was no significant difference between the two groups in terms of age, the initial size of effusion, or the interval between the two aspirations before entry into the study.

The results of intrapleural therapy are shown in table 2. All patients treated with mustine experienced nausea and 11 of the 12 vomited, in some cases repeatedly. These symptoms were only partially controlled by antiemetics such as cyclizine and metoclopramide. In contrast only one of nine patients treated with *C parvum* was nauseated while one experienced a mild fever at 38°C. Four patients, deemed mustine failures, subsequently treated with *C parvum* had no reaction.

Three patients died within three weeks of initial intrapleural therapy. In the *C parvum*

group two patients died of massive pulmonary emboli and in the mustine group one patient died after 21 days from his disseminated malignant disease. The survival of these patients was too short to assess any suppression of pleural fluid reaccumulation. Of the remaining 11 patients treated initially in the mustine group, five were a complete success, one a partial success in view of the requirement for a further aspiration and repeat instillation of mustine, and five were failures as repeated aspirations were required. Four of these patients were subsequently treated with intrapleural *C parvum*, with complete success in three cases, the fourth patient's survival being too short to assess a response adequately.

Of the remaining seven patients in the *C parvum* group, five were a complete success and two a partial success as a result of the necessity for repeat aspiration and reinstillation of *C parvum*. In one of these patients a hydropneumothorax necessitated prolonged intercostal drainage. There were no failures. As already described, of the four patients deemed mustine failures, three responded well and were clearly successes. when subsequently treated with *C parvum*. These four patients, all with underlying bronchogenic carcinomas, had recurrent effusions despite two doses of intrapleural mustine, reaccumulating an average 5.8 litres over a mean of 24 days. In all four patients a single dose of *C parvum* resulted in no further aspirations being required, the patients surviving a further 73 days mean (range 21–125 days).

Table 1 *Patient data*

Treatment	Number of patients	Mean age (yr)	Sex	Histology	Initial aspirate volume (litres)	Interval between aspirations before therapy (days)
Mustine	12	66·5	10M 2F	Lung (9) Colon (1) Bladder (1) Ovary (1)	3·1	11·5
C parvum	9	70	4M 5F	Lung (7) Kidney (1) Breast (1)	2·9	15·5

Table 2 *Results of intrapleural therapy*

	Number of patients	Insufficient survival to assess	Assessment of response*			Local reaction	Mean survival (days)
			Success	Partial success	Failure		
Mustine	12	1	5	1	5	Nausea (12) Vomiting (11)	86
C parvum	9	2	5	2	0	Nausea (1) Fever 38°C (1)	80
Mustine failures treated by C parvum	4	1	3	0	0	Nausea (1)	76
Total C parvum	13	2	9	2	0	Fever 38° C (1)	79

*For definition see text

There was no difference in overall survival in the two groups, the mean survival in days being 86 for the mustine group and 80 in the *C parvum* group at the time of analysis when three patients treated by mustine alone and four patients by *C parvum* alone were still alive.

Postmortem examination of three patients treated with *C parvum* showed extensive fibrinous exudate, adhesions, and fibrosis with obliteration of the pleural cavity in some patients as described by Webb.[8]

Discussion

Many new agents have been reported over the last few decades as being effective by intra-pleural injection in the suppression of recurrent malignant effusions, but only rarely has a direct comparison been made with an established thera-peutic agent. Most agents inducing a chemical pleurodesis are successful in 50–70% of patients while the more invasive procedure of surgical pleurodesis is more effective. The recent interest in the immunological influences on intrathoracic tumour growth has led to the assessment of active immunological agents in the suppression of malignant effusions. *Corynebacterium parvum* has proved a potent immunological agent in advanced disseminated cancer.[9] When first re-ported by Webb *et al*[8] as an intrapleural and intraperitoneal agent, *C parvum* was successful in six patients and described as being of un-doubted use in the management of malignant effusions and ascites. Our experience in a com-parative study of *C parvum* and mustine certainly supports this view, and we conclude that *C parvum* is a better tolerated and more effective suppressive agent than mustine. No major untoward side-effects were noted with *C parvum,* and the overall survival of the two treated groups of patients was similar. The mechanism of action of *C parvum* is uncertain. It certainly induces a pleurodesis with dense fibrosis in the pleural cavity but the relative contributions of chemical irritation and immuno-logical reaction are unclear. The apparent superiority of *C parvum* over mustine, a proven

cytotoxic agent acting by chemical pleurodesis, suggests that the immunological response trig-gered by *C parvum* may be of importance in its action. Webb *et al*[8] showed that the average count of malignant cells in pleural and ascitic fluid in their patients was reduced by *C parvum* and this may suggest a direct immunological sup-pression of tumour cells. We plan to investigate this further by measuring *C parvum* antibody responses in both plasma and pleural fluid in treated patients and to correlate this with the clinical response.

References

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