

SCLEROTHERAPY FOR MALIGNANT PLEURAL EFFUSIONS- A PROSPECTIVE RANDOMIZED TRIAL OF VINCRISTINE VERSUS CISPLATIN

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ABSTRACT

BACKGROUND

Malignant pleural effusions are a common cause of morbidity in patients with advanced cancer. Cancer of the lung breast and lymphomas account for approximately 75 % of malignant pleural effusions. Sarcomas and melanomas account for a small percentage of malignant pleural effusion. In about 6 % of patients the primary is unknown.

The aim of the study is to evaluate the efficacy of pleurodesis using Vincristine and Cisplatin and to compare the outcomes of pleurodesis with these two sclerosing agents in malignant pleural effusions.

MATERIALS AND METHODS

All patients with malignant pleural effusion were evaluated and patients with previous sclerotherapy, hepatic or renal dysfunction were excluded. Patients eligible for pleurodesis were randomized by "Randomisation by Blocking" technique into two groups. They received either Vincristine (2 mgs/m²) or Cisplatin (70 mgs/m²) intrapleurally through the intercostal tube as per BTS guidelines on management of malignant pleural effusions. Patients were evaluated for response after four weeks.

Design- Prospective randomized clinical trial.

RESULTS

48 cases of malignant pleural effusions were evaluated. 30 cases were excluded for reasons for reasons such as rapid progression of the disease(13), non expansion of lung (15) and not willing for further treatment(2). 18 eligible patients were included for the study and randomized to receive either Vincristine or Cisplatin. Out of 10 patients who received Vincristine sclerotherapy, complete response was noted in 60 % and objective response (complete plus partial responses) in 70 %. Out of 8 patients who received Cisplatin sclerotherapy, complete and objective response was noted in 87.5 %. There was no significant differences in response rates between Vincristine and Cisplatin either in complete response ($p = 0.315$) or in objective response ($p = 0.588$).

CONCLUSION

Both Vincristine and Cisplatin are effective sclerosing agents in malignant pleural effusions, though neither agent was superior to the other in this study. Since Vincristine is cheaper, it is more cost effective agent for pleurodesis in malignant pleural effusions.

KEYWORDS

Pleurodesis, Sclerotherapy, Vincristine, Cisplatin, Malignant Pleural Effusion.

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BACKGROUND

Malignant pleural effusions are a common cause of morbidity in patients with advanced cancer. Cancer of the lung breast and lymphomas account for approximately 75 % of malignant pleural effusions. Sarcomas and melanomas account for a small percentage of malignant pleural effusion. In about 6 % of patients the primary is unknown.¹

Most patients with malignant pleural effusion present with progressive dyspnoea, cough or chest pain that compromise the quality of remaining short life of these

patients. The prognosis of these patients is poor and mean survival after confirming the diagnosis is approximately three months.²

Treatment options depend on a number of factors such as cell type, extent of disease, performance status and life expectancy.³ Intervention options range from observation in case of asymptomatic effusions through simple thoracentesis to more invasive procedures such as thoracoscopy, pleuroperitoneal shunting and pleurectomy⁴

In patients with reasonable survival expectancy and good performance status every attempt should be made to prevent recurrence of effusion.⁵ In most cases malignant pleural effusion is controlled by tube drainage combined with pleurodesis.⁶ This is also the most cost effective method as shown by Belani and his colleagues.⁷

Successful sclerotherapy depends on variety of technical and clinical features such as tube size, sclerosing agent, the amount of initial pleural fluid and tumour burden.³ Given all

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these variables there is no uniform agreement as to the most effective treatment protocol for malignant pleural effusion.

A wide range of sclerosants have been tried after drainage including Tetracycline, Quinacrine, Talc, Adriamycin, Bleomycin, Nitrogen mustard and more recently Vincristine and Cisplatin. However there are few randomised trials comparing any of these agents. ⁸

Although Talc, parenteral Tetracycline and Bleomycin are the most widely used agents for pleurodesis, parenteral Tetracyclines are not freely available worldwide, Bleomycin is expensive and concerns about the safety of Talc are growing.⁹

This prospective randomized study was done to determine the efficacy of pleurodesis with two agents Vincristine and Cisplatin and to compare the outcomes of these two. These two drugs were taken up for study after taking into account the local availability, the ease of administration and the cost of treatment with these agents.

Aims and objectives

1. To evaluate the efficacy of pleurodesis using Vincristine.
2. To evaluate the efficacy of pleurodesis using Cisplatin.
3. To compare the outcome of pleurodesis using Vincristine and Cisplatin.

MATERIALS AND METHODS

This study was a prospective randomized clinical trial to compare intrapleural Cisplatin and Vincristine as sclerosing agents in the treatment of malignant pleural effusions. The entire study was done by a single investigator. Institutional ethical committee approval was granted for the study. All patients with malignant pleural effusion were taken up for the study. These patients were on treatment for their primary malignancy as per standard protocols. Patients with previous sclerotherapy and patients with hepatic or renal dysfunction were excluded from this study. Patients were randomised by the 'randomization by blocking' method. The sclerotherapy protocol followed was as per the BTS guidelines on management of malignant pleural effusion.⁴ Only a single sitting of pleurodesis was done after ensuring adequate apposition of the pleural layers.

Patients were followed up with Chest Radiograph after four Weeks after Pleurodesis and Responses were classified as-

- a. Complete response – No clinical or radiological recurrence of pleural effusion.
- b. Partial response- Small amount of fluid reaccumulation in chest radiograph but no symptoms.
- c. Failure – Reaccumulation of fluid causing symptoms or needing thoracocentesis.

RESULTS

During the study period, 48 cases of malignant pleural effusion were identified. Out of 48, 30 patients could not be taken up for the study because of reasons such as rapid progression of the disease in 13 patients, non expansion of the lung in 15 patients, not willing for treatment in 2 patients

Included for the study		18
Excluded from the study		30
Rapid progression of disease	13	
Non expansion of the lung	15	
Not willing for further treatment	2	
Total number of cases		48

Table 1. Summary of Total cases screened

The remaining 18 patients were included in the study. They had been diagnosed as malignant pleural effusion by pleural fluid cytology alone in 12/18 patients (67%), pleural biopsy alone in 4/18 (22%) and by both in 2/18 (11%).

Out of 18 patients, 9 (50%) had right sided pleural effusion and 9 patients(50%) had left sided pleural effusions. 11/18 patients (61%) had massive effusions and 7/18 (39%) had moderate effusions. In 12/18 patients (67%) the effusions were bloody while in 5/18 serosanguinous and 1/18 (5%) had serous effusion.

They were randomised to receive either Vincristine or Cisplatin and treated as per protocol. Out of 18 patients, 10 patients received Vincristine and 8 patients received Cisplatin.

The demographic characteristics of these two treatment groups are summarized in Table 2. The mean age of the patients was 46.2 years in Vincristine group and 63.7 years in Cisplatin group. The male: female ratio in the Vincristine group was 2:8 and in Cisplatin group 6:2.

		Vincristine (n=10)	Cisplatin (n=8)	
Age Years	Mean	46.2	63.7	p= 0.03
	(Range)	(27-60)	(46-78)	
Sex	Male	2 (20%)	6 (75%)	p = 0.054
	Female	8 (80%)	2 (25%)	

Table 2. Demographic characteristics of patients in two treatment groups

This table shows that the two groups showed statistically significant difference with regards to age but not with sex distribution

The primary site of malignancy in the two treatment groups are summarized in Table 3. It was found that the majority of patients in the study group has lung cancer in 6/18(33%) followed by breast in 5/18(28%), ovary, thyroid and anal canal one each (17%). The primary site of malignancy was unknown in 4/18(22%)

Primary Site of Malignancy	Vincristine (n = 10)	Cisplatin (n= 8)
Anal canal		1 (12.5%)
Breast	5 (50%)	
Lung	2 (20%)	4(50%)
Ovary	1(10%)	
Thyroid		1(12.5%)
Unknown	2 (20%)	2(20%)

Table 3. Primary site of malignancy of patients in the two treatment groups

Patients were evaluated for the outcome of pleurodesis after four weeks using chest radiograph and the results were graded as complete response, partial response and failure. The outcome of pleurodesis in the Vincristine group is summarized in table 4.

	Vincristine (n=10)
Complete Response	6(60%)
Partial response	1(10%)
Failure	1(10%)
Lost to follow up	1(10%)
Died	1(10%)

Table 4. Outcome of Pleurodesis using Vincristine

Complete response was observed in 60% of patients, partial response in 10%, failure of pleurodesis in 10%. One patient was lost to follow up and one died before evaluation of the response.

The outcome of pleurodesis in Cisplatin group is summarised in table 5.

	Cisplatin (n=8)
Complete response	7(87.5%)
Partial response	-
Failure	-
Lost to follow up	1(12.5%)
Died	-

Table 5. Outcome of response using Cisplatin

Complete response was observed in 87.5% of patients and one patient was lost to follow up. None of the patients who received Cisplatin showed partial response.

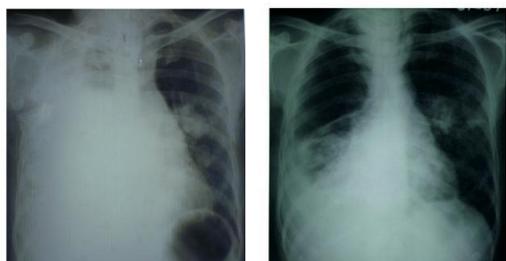
	Vincristine	Cisplatin	p value
Complete response	60%	87.5%	0.314
Objective response (complete response + partial response)	70%	87.5%	0.588

Table 6. Shows the response rate in the two groups

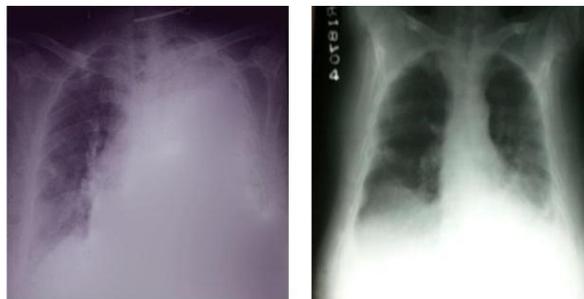
The complete response rate was 60 % with Vincristine and 87.5 % with Cisplatin. The objective treatment response rate (complete response plus partial response) in the two groups was 70 % with Vincristine and 87.5 % with Cisplatin.

No adverse events were recorded during the sclerotherapy with these two agents.

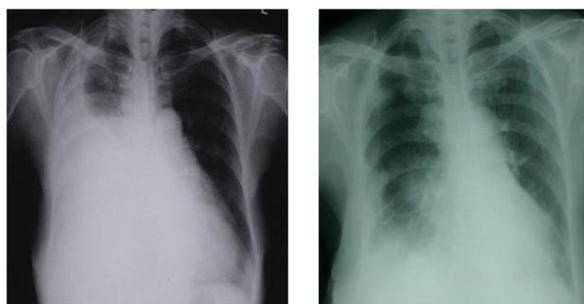
Chest radiographs of malignant pleural effusions before and after pleurodesis



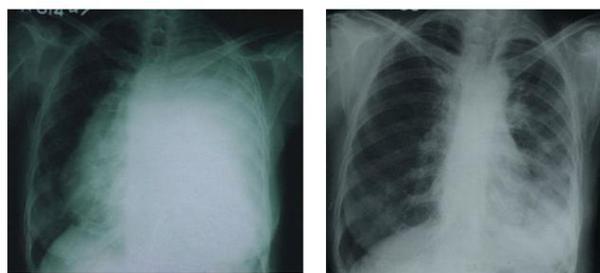
Metastatic Thyroid cancer



Metastatic Ovarian cancer



Metastatic Anal canal cancer



Metastatic unknown primary

DISCUSSION

Malignant pleural effusions remain a distressingly common complication of advanced cancer. Excluding patients with highly and potentially responsive tumours like Lymphoma, small cell lung cancers and Ovarian cancers (and excluding moribund patients), there still remain a large number of patients with symptomatic effusions who require palliative treatment with tube thoracostomy and intrapleural therapy.¹

This study was taken up to assess the outcome of pleurodesis using Vincristine and Cisplatin and to compare the outcome of pleurodesis using these two agents. These agents were taken up for study based on the easy local availability, the cost and the ease of administration of these drugs.

Forty eight patients with proven malignant pleural effusions were examined and investigated as per the prestructured proforma after their written informed consent.

Out of 48, 30 patients had to be excluded from the study due to reasons such as rapid progression of the disease in

13, non expansion of the lung in 15 and not willing for further treatment in 2 cases (Table 1). So it is observed that, even after excluding patients not willing for further treatment, many patients with malignant pleural effusion cannot be subjected to pleurodesis.

Eighteen patients were included for the study. They were randomized to receive either Vincristine or Cisplatin. Using the block randomization technique, 10 patients had received Vincristine and 8 had received Cisplatin. Patients were evaluated for outcome of pleurodesis after four weeks using chest radiography and the results were graded as complete response, partial response and failure.

Complete response was obtained in 60 % and objective response in 70 % of patients who had received Vincristine and in 87.5 % of patients who had received Cisplatin. This shows that both Vincristine and Cisplatin can be used as effective sclerosing agents for pleurodesis in malignant pleural effusion.

No adverse events were recorded during sclerotherapy with these two agents which shows that these agents can be safely used for pleurodesis.

There is no statistical significance observed in the outcome of response rates when comparing Vincristine and Cisplatin as sclerosing agents in malignant pleural effusions. So it is inferred that neither Vincristine nor Cisplatin have any superiority over each other as sclerosing agents. Since cost wise, Vincristine is cheaper than Cisplatin, Vincristine is a more cost effective alternative for pleurodesis in malignant pleural effusions.

CONCLUSION

It is concluded from the above study that both Vincristine and Cisplatin are effective sclerosing agents in pleurodesis

though the superiority of either of these two could not be ascertained. Since Vincristine is cheaper, it would be a more cost effective sclerosing agent for pleurodesis in malignant pleural effusion.

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