

Interferon α -2a in Combination with Cisplatin in the Treatment of Diffuse Malignant Pleural Mesothelioma

NIVINE M.A. GADO, M.D.

Radiation Oncology, Nuclear Medicine Department, Ain Shams University.

ABSTRACT

Purpose: This study was planned to evaluate the objective response rate of Interferon α -2a in combination with cisplatin in treatment of newly diagnosed patients of diffuse malignant pleural mesothelioma.

Patients and methods: Twenty-six patients with diffuse malignant pleural mesothelioma were treated by immunotherapy with interferon (IFN) in combination with chemotherapy (cisplatin). Cisplatin was given at a dose of 60 mg/m², day 2 and IFN α -2a (6MU/d, days 1-4) in a protocol of 4 weeks on and 4 weeks off followed by 3 weeks on and 3 weeks off. In responders, IFN as maintenance was continued for a further of 6 months. Six patients were stage II, seventeen stage III and three stage IV according to the International Union Against Cancer staging system.

Results: Nine patients (34.6%) achieved an objective partial response; thirteen (50%) had stationary disease and the disease progressed in four (14.4%). All patients were assessed for toxicity. Hematological toxicity was the most common, but was manageable followed by grade 1 renal toxicity.

Conclusion: The combination of interferon α -2a and cisplatin is still not the standard treatment of malignant pleural mesothelioma. Further studies should be carried on to reach better response rates against this aggressive tumor that has an increasing incidence.

Key Words: IFN- α - Cisplatin - Pleural mesothelioma.

INTRODUCTION

Malignant mesothelioma is an aggressive tumor arising from serous surfaces. Diffuse malignant pleural mesothelioma (DMPM) is locally aggressive, invasive and almost invariably fatal [28]. The major unprotected asbestos use from 1940s through 1960s lead to increased incidence of DMPH [15]. The incidence of this aggressive tumor is still increasing. In most reports, the median survival time for patients with this disease is not >1 year [27].

In Egypt at the department of Radiation Oncology & Nuclear Medicine Ain Shams University, the frequency of malignant mesothelioma is increasing. In 1996, it was 1.45% of total number of cases at the department & it increased to reach 3% in 2000 [10].

The treatment of DMPM is currently less than satisfactory [11].

Standard anticancer drugs have low response rates. To date, no regimen has been suggested as a standard therapy for DMPM [22]. Therefore, the role of chemotherapy in the management of DMPM continues to be a subject of investigation [22].

Immunotherapy with interferon (IFN) is a systemic approach to the treatment of DMPM. The anti proliferative activity of IFN has been used in some human tumors such as hairy cell leukemia, lymphoma and renal cell carcinoma [18]. Also, IFN augments surface HLA antigen expression in malignant mesothelioma cell lines. Moreover, interferons were shown to be active on those mesothelioma cell lines in which anti-neoplastic drugs were ineffective [23]. Marked increase in activity of various chemotherapeutic agents by IFN was demonstrated in human malignant mesothelioma xenografts in mice or in mesothelioma cell lines [23].

In 1996, Soulie et al. [26] showed 40% response rate with CDDP (60 mg/m²) and IFN α -2a (3MUx4) in combination therapy for advanced diffuse malignant mesothelioma. As IFN action is dose dependent, so a higher dose of IFN in combination with same dose of CDDP as that studied by Soulie et al. was used in this study.

PATIENTS AND METHODS

Patients:

Twenty-six patients with histologically proven DMPM were enrolled in this study from December 1999 to April 2002. The characteristics of evaluable patients are shown in table (1).

The eligibility criteria for all study cases were as follows: (1) Age younger than 75 years old (2) Performance status ≤ 2 as defined by the Eastern Cooperative Oncology Group (ECOG); (3) A normal bone marrow function as defined by a total leucocyte count $\geq 3500/\text{mm}^3$, a hemoglobin concentration $> 10\text{g/dL}$, neutrophil count $\geq 1500/\text{mm}^3$ and a platelet count $\geq 100000/\text{mm}^3$, (4) Normal renal function as defined by a creatinine clearance $> 60\text{ ml/min}$. and a normal hepatic function as defined by less than twice the upper normal limit (5) Previously untreated patients with histologically and immunohistochemically confirmed malignant mesothelioma of the pleura with a measurable unidimensionable disease by computed tomography (CT) scan. Pleural effusion wasn't considered as a measurable or evaluable disease.

Patients classified as stage I malignant pleural mesothelioma and those with life expectancy of less than 3 months were excluded.

After the histopathologic diagnosis was made, all patients were classified according to the International Union Against Cancer staging system.

Table (1): Characteristics of patients with histologically proven DMPM.

Characteristics	No. of patients
Mean age, yr (range)	55.4 (26-75)
Gender: Male	12
Female	14
Stage, No. of patients (%):	
II	6 (23)
III	17 (65)
IV	3 (12)
Histopathologic subtype, No. of patients (%):	
Epithelial	13 (50)
Mixed	7 (27)
Sarcomatous	4 (15)
Unidentified	2 (8)
Mean performance status by ECOG (range)	1 (0-2)
Smoking No. of patients (%)	21 (81)
Mean symptom durations no (range)	3.6 (0.5-12)

Drug schedule

No.of weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
	1st cycle				Rest				2nd cycle				Rest				3rd cycle			Rest			4th cycle		

In responders maintenance for 6 Ms. by IF- α -2a S.C. 3d/week.

Treatment was delivered on a weekly schedule in four cycles. The first two cycles consisted of 4 weeks of treatment each, separated by 4 weeks of rest. After the second cycle, there was another period of 4 weeks rest. The third and fourth cycles lasted 3 weeks each, separated by 3 weeks of rest. Total duration of treatment was thus 25 weeks. In responders, treatment with IFN α -2a was continued as monotherapy 3 days per week for 6 months.

During each weekly schedule, cisplatin (CDDP) (60 mg/m²) was administered on day 2 of the week. IFN α -2a, 6MU/day was administered subcutaneously on days 1-4 of each week of treatment. Patients were hospitalized on day 2 for pre- and post-CDDP hydration therapy, electrolyte replacement and anti-emetics. The infusion schedule consisted of:

(1) Prehydration with 2000 ml of 5% dextrose, 6g NaCl and 3gKCl administered over 6

h. One gram of MgSO₄ was added to the first liter and 1.375 g of calcium was added to the second liter of dextrose solution; (2) 8 mg of ondansetron in 50 ml of normal saline over 15 min and 120 mg methylprednisolone as intravenous bolus 30 min. before CDDP; (3) CDDP powder dissolved in 500 ml of normal saline over 2h. (4) at the end of CDDP infusion 250 ml of mannitol was infused over 15 min; and finally, (5) post hydration similar to prehydration infused over 8 h.

Before each course of treatment, the patients underwent complete physical examination, complete blood picture and serum hepatic and renal functions to evaluate toxicity.

Evaluation of response:

The patients were assessed for response 4 weeks after the last dose of CDDP of each of the first two cycles and at the end of treatment. Assessment was done by a thoracic CT scan.

The length and breadth of the tumor at the site of maximum thickness were measured on the initial scan and compared at the same level on follow-up scans. The response was classified as complete response (CR), partial response (PR), stable disease (SD) or progression (PD) according to WHO criteria.

A complete response (CR) was defined as complete disappearance of all measurable disease for 4 weeks or more without the appearance of new lesions. A partial response (PR) was defined as a greater than or equal to 50% decrease in the sum of the products of the tumours' longest dimension and its widest perpendicular measurement compared to pretreatment measurements lasting for 4 weeks during which no new lesion appeared and no existing lesions enlarged. Stable disease (SD) was defined as either no change, less than 50% reduction or no more than 25% increase in tumor size; and progressive disease (PD) was considered if a new lesion appeared or any measurable increase in tumor size.

Duration of survival and response were calculated from the time of beginning of treatment to the present date (i.e. April 2002 if the patient was alive; or until the time of death). Time to progression was estimated from the start of treatment till the first sign of progression.

After treatment with CDDP + IFN or during IFN maintenance therapy, patients were followed up monthly with a clinical examination and a chest x-ray.

Statistical analysis:

The duration of survival and the median survival times [95% confidence interval (CI)] were estimated according to the Kaplan-Meier method.

RESULTS

Starting from December 1999, twenty-six patients with DMPM were monitored until the end of the study in April 2002. Fourteen patients presented by dyspnea and fourteen had chest pain on the side of the disease, eight had a dry cough and four patients had anorexia and weight loss. Needless to mention that most of the patients suffered from more than one symptom. The material for diagnosis was obtained by transthoracic needle biopsy of the pleura.

Overall, 100 cycles were administered, with a median of 3 cycles per patient and a range of 2 to 4 cycles. Twenty-six patients successfully completed all four cycles. Among them, eleven patients received maintenance IFN therapy; ten for 6 months and one for 3 months. The cause of premature stoppage of treatment was drug toxicity.

The median total cumulative dose of CDDP was 596 mg/m² range (114-861). For IFN α -2a, it was 264 MU (range 72-336). On average, 56.3 mg/m² (median 57.6, range 45.5-61.5) of CDDP was administered with an average dose intensity of 31.1 mg/m²/week (median 29.5, range 21.4-54.3).

Objective response and survival:

Nine patients (34.6%) achieved an objective partial response; thirteen (50%) had stationary disease and the disease progressed in four (14.4%). All responding patients did so within two cycles.

Most of the 9 PR patients were stage II (five patients), the other four patients one was stage IV and three patients were stage III. Six patients of the PR were of epithelial type and 3 were of mixed type. Table (2) shows the relationship of response to stage and histopathology.

Table (2): Relationship of response to stage and histopathology.

Response	CR	PR	SD	PD	Total No. of patients
<i>Stage:</i>					
II	—	5			5
III	—	3	12	1	16
IV		1	1	3	5
<i>Pathology:</i>					
Ep.	—	6	6		12
Mixed	—	3	3		6
Sarcomatous			1	2	3
Unidentified			3	2	5
Total	—	9	13	4	—

The median survival time for all patients was 16.5 months (confidence interval (CI) 10.4-30.3 and 1- and 2-year survival rates were 75% and 27% respectively (Fig. 1). Median time to progression was 6.4 months (CI 4.6-11.8) (Fig. 2).

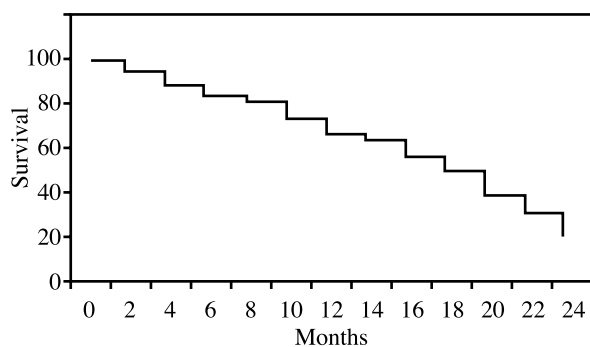


Fig. (1): Overall survival.

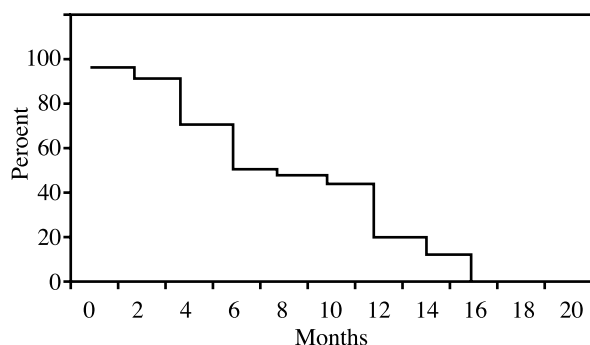


Fig. (2): Time to progression.

Toxicity:

Treatment was well tolerated, hematological toxicity was most frequently observed and consisted of anemia, neutropenia and thrombocytopenia (Table 3). Gastrointestinal and asthenia were the nonhematological toxicity. Renal toxicity was moderate (grade 1 in twelve patients). The manifestations of gastrointestinal toxicity, anorexia, nausea and vomiting were observed in twelve patients (46%). Grade 1 polyneuropathy was observed in four patients. Twelve patients experienced asthenia, grade 3 in eight of them and grade 2 in four. Classical flu-like symptoms were observed in eight patients which was controlled on paracetamol.

Table (3): Number of patient toxicity according to the world health organization scale.

Toxicity	Grade			
	1	2	3	4
Anemia	6	6	10	0
Thrombocytopenia	6	6	2	4
Neutropenia	4	10	8	2
Renal	12	0	0	0
Gastrointestinal	0	4	8	0
Polyneuropathy	4	0	0	0
Asthenia	0	4	8	0

In general, twelve patients showed improvement of their symptoms. Chest pain was the first symptom to disappear in ten out of fourteen patients. Eight out of fourteen patients had improvement in dyspnea; however, none of the patients gained the initial weight loss.

DISCUSSION

At present there is no standard therapy for malignant pleural mesothelioma at any stage of disease [20]. A limited number of patients with small volume disease and good performance status can be considered for extrapleural pneumonectomy [21].

The delivery of radical doses of radiotherapy is limited by the extensive nature of mesothelioma and the consequent risk of lung and adjacent organ damage [8].

In recent years, however, it has been claimed that an aggressive surgical treatment, extrapleural pneumonectomy, for which a limited number of patients are usually eligible, results in only a modest improvement in overall survival. In a multimodality approach that included pleuro pneumonectomy, chemotherapy and radiotherapy, 2-year and 5-year survival rates for the entire cohort were 45% and 22%, respectively, with a median survival time of 21 months among the patients without mediastinal and transdiaphragmatic involvement [27]. In another study, multimodality treatment of 49 non-measurable patients with Butchart stage IDMPM resulted in a median survival time of 22 months and a 3-year survival rate of 34% [2].

Most of the patients with DMPM present with unresectable disease. Thus, systemic therapy is considered the only treatment option for them [27]. Various trials of chemotherapeutic agents have been performed over the years, but few have shown clear benefit; most of the studies were too small in scale to accurately measure the responses. Additional problems include heterogeneity of the patient populations, use of second-line drugs, and a possibility of erroneous pathologic diagnosis [11].

Of the chemotherapy agents that have been studied, anthracyclines, platinum compounds, and alkylating agents have demonstrated small but noteworthy activity against mesothelioma [14]. In all series, cisplatin given at standard doses has shown modest activity, yielding response rates of less than 20% [11].

Blay and Rebattu [4] administered CDDP at a dose of 40 mg/m²/d for 5 consecutive days, every 28 days. They observed a marked decrease in thoracic pain 1 month later and a PR at the end of 2 months (total duration of treatment not mentioned). Planting et al. [16] administered CDDP as a monotherapy at a dose of 80 mg/m²/week for 6 weeks. Five of their 14 patients had a PR lasting 2-8 months. They received a mean dose intensity of 69mg/m²/week.

Combinations of chemotherapeutic drugs have also been tested in numerous studies; most have shown no advantage over single agent chemotherapy [11].

In recent years, immunotherapy containing IFNs has shown some success in the treatment of solid tumors. Although all forms of IFN have antiproliferative activity, IFN-alpha has been the most extensively studied. All preclinical studies have suggested that IFN-alpha may display a certain activity in mesothelioma cell lines, by way of a direct inhibitory effect and its capacity to upregulate surface expression of major histocompatibility complex class I molecules involved in tumor recognition [6].

As a single agent, IFN-alpha has been used on a limited number of patients. At dosages that ranged from 3-18 million IU/d, investigators observed only four objective responses out of 25 patients. On the other hand, only marginal activity (1 responder among 13 assessable patients) was seen with the systemic administration of recombinant IFN-alpha 2b [1]. Previous studies have not shown IFN-alpha to be reactive as a single agent in the treatment of DMPM.

Sklarín et al. [24] had shown the moderate activity of cisplatin and mitomycin to be markedly increased by the addition of IFN-alpha in human mesothelioma xenografts. This and other similar findings suggested that it may be possible to enhance the effects of the immunomodulatory or antiproliferative agents to which mesothelioma is partially responsive by combining the chemotherapeutic agents with IFN-alpha. After the study of Sklarín et al. [24] The combination of IFN-alpha and active chemotherapy agents were tried in combinations [12, 17,19,26,29].

Rodier et al. [19] observed only a marginal efficacy for the combination chemotherapy that

consisted of IFN (3MU on days 1-3), CDDP (75 mg/m²) and mitomycin (10 mg/m² on day 2). Tansan et al. [21] and Metintas et al. [12] used a combination of IFN (4.5 Mu2/w), CDDP (30 mg/m² on d1 and 2) and mitomycin (8 mg/m² on day 1) where they found that it was moderately effective and well tolerated especially in those who responded to the treatment. Soulie et al. [26] observed an encouraging 40% response rate in their phase I-II study. They used a combination of CDDP (60 mg/m²/w on day 2) and IFN (3 MU on days 1-4). They observed a median overall survival of 12 months (360 days) and of 25 months (750 days) in responding patients. Purohit et al. [17] used the same drug regimen. Their survival rate was 27% with an overall median survival of 15 months. The results of this study were similar to those of Soulie et al. [26] and Purohit et al. [17] as response rate was (9/26 [34.6%] versus 10/25 [40%] and 5/13 [38.5%] respectively). The overall median survival was a little longer in this study i.e.16.5 months while it was 12 months in Soulie et al.study and 15 months in Purohit et al. [17].

In the series with the multimodality approach [2,27] the median survival times were 21 and 22 months, while in Purohit study the median survival time was 16.5 months. It is worth noting that Purohit study did not include stage I while the multimodality series [2,27] included stage I mainly.

Renal toxicity was, as in the other studies [17, 23], generally limited to transient increase in serum creatinine. Flu-like manifestations due to IFN were prevented by paracetamol.

It is concluded that the drug combinations used in this study was moderately effective and well tolerated in patients with DMPM, especially in responsive patients. Unfortunately, the overall response rate was low and the median survival time was not long enough to consider this treatment to be of general benefit to all DMPM patients. The combination of CDDP and IFN in large doses proved to be feasible. The increase in IFN dose from 3 to 6 MU/day did not seem to increase toxicity, but also did not induce better results. On the other hand, this and other well-defined studies [11,12,17,23] indicated that mesothelioma may not be totally chemotherapy resistant.

Other approaches like high dose methotrexate [25] and gemcitabine either alone or with

CDDP [3,5], in addition to high dose methotrexate in combination with interferons [9] have shown promising results in terms of survival and symptom improvement and need to be evaluated further. It would be interesting to carry out randomized phase II studies, comparing those chemotherapeutic regimens to CDDP-IFN combination.

Recently two antifolate-based combinations with apparently higher efficacy than older regimens have emerged [the premetrexed (Alimta)/cisplatin and the raltitrexed (Tomudex)/oxaliplatin regimen].

In two phase I trials with pemetrexed combined with either cisplatin or carboplatin responses occurred in 5 of 11 (45%) and nine of 29 (31%) respectively. In a phase I trial of raltitrexed/oxaliplatin, 6 of 17 patients (35%) achieved partial response. Based on the promising results from these combination trials, two large phase III studies have begun. In both trials, survival was the main endpoint. These trials will help to define the role of these new antifolate in malignant pleural mesothelioma [7].

Ranpirnase (OncoSase), a novel antitumor ribonuclease, was assessed in a multicenter phase II trial as a single agent in patient with unresectable mesothelioma. 1 and 2 year survival rates were 42% and 26.8% respectively [13].

REFERENCES

- 1- ARDIZZONI A., PENUCCI M.C. and CASTAGNETO B.: Recombinant interferon alpha-2b in the treatment of diffuse malignant pleural mesothelioma. *Am. J. Clin. Oncol.*, 17: 80-82, 1994.
- 2- BALDINI E.H., RECHT A., STRAUSS G.M. and DE CAMP M.: Patterns of failure after trimodality therapy for malignant pleural mesothelioma. *Ann. thorac Surg.*, 63: 334-338, 1997.
- 3- BISCHAFF H.G., MANEGOLD C., KNOPP M., BLATTER J. and DINGS P.: Gemcitabine (Gemzar) may reduce tumor load and tumor associated symptoms in malignant pleural mesothelioma. *Proc. Am. Soc. Clin. Oncol. Abstract (ASCO)*, 17: 464a, 1998.
- 4- BLAY J.Y. and REBATTU P.: Interet du cis-platinum a forte dose dans le traitement du mesotheliome malin pleural. *Rev. Pneumol. Clin.*, 44: 54-58, 1998.
- 5- BYRNE M.J., DAIRDSON J.A., MUSK A.W., DEWAR J., VAN HAZEL G., BUCK M., DE KLERK N. and ROBINSON B.W.S.: Cisplatin (C) and Gemcitabine (G) treatment of malignant mesothelioma: a phase II study. *Proc. Am. Soc. Clin. Oncol. Abstract (ASCO)*, 17: 464a, 1998.
- 6- CHRISTMAS T.I., MANNING L.S. and GARLEPP M.J.: Effect of interferon alpha 2a on malignant mesothelioma. *J. Interferon Res.*, 13: 9-12, 1998.
- 7- FIZAZI K., JOHN W. and VOGELZANG N.: The emerging role of antifolates in the treatment of malignant pleural mesothelioma. *Semin-Oncol.* Feb., 29 (1): 77-81, 2002.
- 8- GORDON W., ANTMAN K., BREEN BERGER, SANDISON A. and FALKSON G.: Radiation therapy in the management of patients with mesothelioma. *Int. J. Radiat Oncol. Biol. Phys.*, 8, 19-24: 1991.
- 9- HALME M., KNUTTILA A., VEHNNAS T., TALMILEHTO L., MANTGLA M., SALO J. and MATTSO K.: High dose methotrexate in combination with interferons in the treatment of malignant pleural mesothelioma. *Br J. Cancer*, 80 (11), 1781-1785. 1999.
- 10- ISMAIL S.S., EL BOUHY M.S., ABD EL-HAFEEZ Z.M. and GHALI R.R.Y.: Clinico-epidemiological study in malignant pleural mesothelioma. Published thesis for Master Degree Dept. of Radiation Oncology Nuclear Medicine, Ain Shams University. 2001.
- 11- MANEGOLD C. and AISNER J.: Pemetrexed for diffuse malignant pleural mesothelioma. *Semin-Oncol.* (suppl 5): 30-35. 2002
- 12- METINTAS M., OZDEMIR N., UCGUN I., ELBEK O., KOLSUZ M., MUTLU S. and METINTAS S.: Cisplatin, Mitomycin, and interferon- α -2a combination chemoimmunotherapy in the treatment of diffuse malignant pleural mesothelioma. *Chest.*, 116, 2: 391-98, 1999.
- 13- MIKULSKI S., COSTANZI J., VOGELZANG N., McCACHREN S., TAUB R., CHUN H., MITTLELMAN A., PANELLA T., PUCCIO C., FINE R. and SHOGEN K.: Phase II trial f a single weekly intravenous dose of ranpirnase in patients with unresectable malignant mesothelioma. *J. Clin. Oncol.* Jan., 20 (1): 274-81, 2002.
- 14- ORG S.T. and VOGELZANG N.J.: Chemotherapy in malignant pleural mesothelioma: a review. *J. Clin. Oncol.*, 14: 1007-1017, 1996.
- 15- PETO J., HODGSON J.T., MATTHEWS F.E. and JONES J.R.: Continuing increase in mesothelioma mortality in Britain. *Lancet*, 345: 535-539, 1995.
- 16- PLANTING A.S.T., SCHELLENS J.H.M., GOEY S.H., VAN DER BURG M.E.L., DE BOER DENERT M., STOTER G. and VERWEIJ J.: Weekly high-dose cisplatin in malignant pleural mesothelioma. *Ann. Oncol.*, 5: 373-374, 1991.
- 17- PUROHIT A., MOREAU L., DIETEMANN A., SEIBERT R., PAULI G., WIHLM J.M. and QUOIX E.: Weekly systemic combination of cisplatin and interferon α 2a in diffuse malignant pleural mesothelioma. *Lung Cancer*, 22: 119-25, 1998.
- 18- QUESADA J.R., REUBAN J., MANNING J.T., HERSH E.M. and GUTTERMAN J.U.: Alfa interferon for induction of remission in hairy cell leukemia. *New Engl J. Med.*, 310: 15-18, 1984.

- 19- RODIER J.M., COUTEAU C., RUFFIE P., TERRIER P., LE CHEVALIER T. and ARMAND J.P.: Phase II study of a monthly combination of cisplatin, mitomycin and interferon Alfa in malignant pleural mesothelioma. *Proc. Am. Soc. Clin. Oncol.*, 15: 390-396, 1996.
- 20- RUSCH V.W. and FIGLIN R.A.: Pleural Mesothelioma. In Haskell CM with contributors, and Berek JS (eds.) *Cancer treatment*. 5th edition W.B. Saunders company, 421-425. 2000.
- 21- RUSCH V.W., PIANTADOSI and HOLMES E.C.: The role of extrapleural pneumonectomy in malignant pleural mesothelioma. *A Lung Cancer Study Group trial: J. Thoracic Cardiovasc Surg.*, 102: 1-9, 1994.
- 22- RYAN C.W., HERNDON J. and VOGELZANG N.J.: A review of chemotherapy trials for malignant mesothelioma. *Chest*, 113 (Suppl.), 66S-73S, 1998.
- 23- SEXL V., WAGNER L., WIESHOLZER M., PRESTERL E. and BASE W.: Treatment of a patient with malignant mesothelioma with interferon alpha 2 based on in vitro sensitivity tests. *Clin. Invest.*, 72: 317-320, 1994.
- 24- SKLARIN N.T., CHAKINIAN A.P. and FEVER E.J.: Augmentation of activity of cisdiaminodichloroplatinum (II) and mitomycin C by interferon in human malignant xenografts in nude mice. *Cancer Res.*, 48: 64-67, 1988.
- 25- SOLHEIM O.P., SAETER G., FINNANGER A.M. and STEINURING A.E.: High dose methotrexate in the treatment of malignant mesothelioma of the pleura. A phase II study. *Br J. Cancer*, 65 (6): 956-960, 1992
- 26- SOULIE P., RUFFIE P., TRANDAFIR L., MONNET I., TARDIVON A., TERRIER P., CIRTKOVIC E., LE CLEVALIER T. and ARMAND J.P.: Combined systemic chemoimmunotherapy in advanced diffuse malignant mesothelioma. Report of a phase I-II study of weekly cisplatin/interferon alfa-2a. *J. Clin. Oncol.*, 14: 878-885, 1996.
- 27- SUGARBAKER D.J. and NORBERTO J.J.: Multimodality management of malignant pleural mesothelioma, *Chest*; 113 (Suppl.), 61S-65S, 1998.
- 28- SUGARBAKER D.J., NORBERTO J.J. and BUENO R.: Current therapy for mesothelioma. *Cancer Control*, 4: 326-334, 1997.
- 29- TANSAN S., EMRI S. and SELCUK T.: Treatment of malignant pleural mesothelioma with cisplatin, mitomycin C and alpha interferon. *Oncology*, 51: 348-351, 1994.