GENERAL THORACIC SURGERY

ISOLATED LUNG PERFUSION WITH PLATINUM IN THE TREATMENT OF PULMONARY METASTASES FROM SOFT TISSUE SARCOMAS

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A multimodality approach including operation and isolated lung perfusion with platinum was used in six patients with lung metastases from soft tissue sarcomas. Staged thoracotomies were used in two patients with bilateral lesions. The inclusion criteria generally applied for surgical excision were adopted in this study. The pulmonary artery and a portion of the left atrium were isolated from systemic circulation and cannulated. The cannulas were then connected to a perfusion circuit and normothermic isolated lung perfusion was done for 60 minutes. The lung was then flushed and metastasectomy was done. Serial blood (systemic and pulmonary), tissue (normal lung and tumor), and urine samples were obtained for platinum content measurement by flameless atomic absorption spectroscopy. Lung damage was assessed by light and electron microscopy examination and by serial respiratory tests. Isolated lung perfusion was accomplished in all patients without any death, operative complication, or systemic toxicity. After operation, interstitial and alveolar edema developed in two patients (48 hours after treatment), necessitating respiratory support in one case. Total platinum concentrations in pulmonary plasma were about 43 times greater than those in systemic plasma. No differences in platinum concentrations between normal lung and metastatic tissue were found. Thus the proposed isolated lung perfusion technique is feasible and safe enough to be offered as a valid model to study combined chemosurgical approaches in the treatment of lung metastases. (*J Thorac Cardiovasc Surg* 1996; 112:614-22)

Long-term survival has been reported in approximately 20% to 30% of patients with lung metastases from soft tissue sarcomas who underwent pulmonary resection.¹⁻⁴ Chemotherapy has given promising results,^{1,5} but the overall response rate to systemic drug administration remains 20% to 30%

for doxorubicin and 20% to 50% for combination chemotherapy.⁴⁻⁷ These findings would support the need for a multimodality approach to the treatment of pulmonary metastases from soft tissue sarcomas. In such a combined therapeutic program, surgical treatment would decrease the tumor burden by removing the macroscopic component of the disease and chemotherapy would eradicate the microscopic foci.³ The concept of a distant spread phase during which metastases would be restricted to the lung could make metastases from soft tissue sarcomas an ideal model for the application of regional chemotherapy. This administration modality would increase the local biologic effect while reducing systemic toxicity. Thirty-five years ago Pierpont and Blades⁸ and Jacobs, Flexner, and Scott⁹ described methods for isolated single-lung perfusion in the dog. Subsequently, with animal models, Johnston and colleagues¹⁰ demonstrated that isolated lung perfusion is a reproducibly safe technique, causing

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Table I. Clinical and pathologic data

Patient	Age (yr)	Sex	Sarcoma histologic type	Sarcoma location	Disease-free interval (mo)	Pulmonary metastases (No. and site)
1	33	M	Synovial	Knee	137	6 (4R/2L)
2	68	F	Rhabdomyosarcoma	Gluteus	47	2R
3	65	F	Rhabdomyosarcoma	Uterus	26	3L
4	54	F	Angiosarcoma	Thigh	16	14 (5R/9L)
5	53	F	Leiomyosarcoma	Uterus	54	3R
6	61	F	Leiomyosarcoma	Retroperitoneum	73	5L

M, Male; R, right; L, left; F, female.

only mild histologic changes in the treated organ. Two-lung perfusion has been accomplished in a single patient with unresectable epidermoid carcinoma by means of two extracorporeal circuits (for pulmonary and systemic circulation).¹¹ The technique of isolated lung perfusion we used in the present study has been previously developed in our laboratory.¹²

Major end points of the present study were (1) to assess the feasibility, under routine hospital conditions, of a protocol including isolated lung perfusion with platinum and metastasectomy, (2) to evaluate the overall toxicity of the combined therapeutic program, and (3) to define the distribution of platinum in both normal and neoplastic tissues. A minor end point was the assessment of platinum pulmonary toxicity, by investigating the relevant morpho-functional changes.

Methods

To allow clear assessment of the procedure, single-drug therapy was used. In the present study, we used a cisplatin dose (200 mg/m²) similar to the highest dose used in the experimental model (5 mg/kg).¹² Such a drug dosage was selected because a 5 mg/kg dose of platinum proved to cause, in the pig, acute lung changes similar to those induced by lower doses. The study protocol was approved by the Scientific Committee of the National Cancer Institute of Genoa. Patients with histologically confirmed soft tissue sarcomas who had evidence of lung metastases were eligible. Inclusion criteria were (1) age younger than 70 years; (2) performance status from 0 to 1; (3) no demonstrable extrapulmonary metastases; (4) control of the primary tumor; (5) prediction of complete resectability of all known metastatic disease; (6) cardiac and lung reserve consistent with the planned operation; and (7) adequate hematologic, hepatic, and renal function. All patients were informed about the potential benefits and hazards of this experimental treatment and gave their consent. No patient was excluded on the basis of (1) the duration of the interval between treatment of the primary tumor and appearance of neoplastic deposits in the lung or (2) the number and size of pulmonary metastases. Preoperative evaluation included chest roentgenogram,

lung and cardiovascular function evaluation, arterial blood gas measurements, bronchoscopy, computed tomography of the chest and abdomen, ultrasonography and computed tomography (supplemented or not by magnetic resonance imaging) of the primary sarcoma region, and bone scan. Clinical and pathologic data are reported in Table I. Two patients had bilateral lung metastases and underwent staged thoracotomies, with bilateral lung perfusion and metastasis resection, at a 4-week interval.

At the time of the operation, regional chemotherapy was given as the first treatment modality because blood supply was still not compromised by metastasectomy. A muscle-sparing anterolateral thoracotomy at the fifth intercostal space was used. The pulmonary artery and veins were exposed by incision of the pericardium. The left pulmonary artery was dissected free and occluded by a vascular clamp lateral to its origin. The right pulmonary artery was clamped between the ascending aorta and the superior vena cava. The lateral portion of the atrium was freed to allow use of a Satinsky clamp to occlude the atrial chamber draining the veins of the perfused lung. Thus the circulation of the lung to be perfused was completely isolated from the systemic circulation, except for the bronchial blood that flowed into the venous return.

Polypropylene purse-string sutures were placed in the pulmonary artery and the superior pulmonary vein. Care was taken to locate the tip of the venous catheter in the atrial chamber and to avoid venous congestion. The vessels were cannulated by a 16F/18F right-angled perfusion catheter (Bard, Tewksbury, Mass.). Intravenous heparin was given (5000 units) before cannulation. The cannulas were then connected to the perfusion circuit. The circuit mainly consisted of 1/4-inch polyvinylchloride tubing joining the venous drainage cannula to a bubble oxygenator (model D700S Dideco, Mirandola, Italy) connected with a heat exchanger. The bloodstream was driven with a roller pump from the oxygenator to the arterial cannula. A cardiomy reservoir (model D742, Dideco) was included in the circuit just downstream of the oxygenator to make possible the washing phase of the treatment. Venous outflow was obtained by gravity. A bypass was located between the arterial and venous lines to allow exclusion of the patient from the extracorporeal circulation (Fig. 1).

By selection of a temperature of 38° to 39° C on the heat exchanger, the lung perfusion temperature ranged from 37° to 37.5° C. The temperature was monitored with

Fig. 1. Diagram of perfusion circuit. OX, Oxygenator.

thermoprobes positioned in the arterial and venous lines and in the inflow and outflow lines of the oxygenator. The body temperature was continuously checked with an esophageal probe. Though the systemic temperature was always unmodified, the head of the patient was wrapped with a refrigerated cuff, and a water-circulating mattress was located under the patient.

The extracorporeal circuit was primed with polygeline (Haemaccel, Hoechst Ltd., Hounslow, United Kingdom) (500 ml), acetate Ringer's solution (500 ml), tromethamine (250 ml), and heparin (75 mg). The lung perfusion flow rate was monitored with an electromagnetic flow probe and was maintained between 200 and 280 ml/min to prevent the mean pulmonary artery pressure from exceeding 35 mm Hg, in view of findings that high arterial pressure values may cause significant lung damage.¹⁰ Lung perfusion was done for 60 minutes. The even distribution of the perfusate throughout the lung tissue was assessed in two patients by infusion of methylene blue dye, as previously described.⁸ The perfusate pH was maintained between 7.3 and 7.4 by addition of tromethamine. The isolated lung was not ventilated during perfusion, and the perfusate was oxygenated to prevent pulmonary vasoconstriction as a result of hypoxia. At the conclusion of lung perfusion, the perfusate was discarded and the circuit was washed (at the flow rate used during the perfusion) with 4000 ml of lactated Ringer's solution (containing bicarbonate and an antiproteinase) to remove unbound platinum. Blood gas values and the acid-base ratio were kept in the physiologic range. After the cannulas were removed, heparin was reversed with protamine sulfate.

A systematic examination of the entire lung field and the mediastinum was then done. All palpable nodules were removed with the use of stapling devices. Lobectomy was done in one case only, with limited resections being the operation of choice.

Blood samples were collected from the perfusion circuit and from the general circulation before, at completion of, and 15, 30, 45, and 60 minutes after cisplatin infusion for determination of hematocrit, hemoglobin, and blood gas values and acid-base balance. At the same observation times, systemic and pulmonary blood, normal lung parenchyma, neoplastic tissue, and mediastinal node samples were obtained for platinum content measurement and morphologic examination. Only lung metastases smaller than 1 cm were used for pharmacokinetic studies because, in our therapeutic program, lung perfusion was applied to sterilize microscopic residual neoplastic foci. Systemic plasma platinum concentrations were also assessed 6 and 12 hours after treatment. Overall lung function was evaluated before and 10, 30, and 90 days after treatment by means of lung volume and airflow measurements and determination of pulmonary diffusing capacity and arterial blood gas values. Ventilation/perfusion scans were done in three patients 90 days after treatment.

For plasma platinum value determination, blood samples (3 ml) were collected in heparinized tubes and immediately centrifuged. Separation of ultrafilterable (free) platinum from total platinum in the plasma was done by centrifugation through anisotropic, hydrophilic YMT ultrafiltration (Amicon Corp., Lexington, Mass.) membranes (molecular weight cutoff: 30,000) in a Micro-partition System instrument (Amicon Corp., Lexington,

Mass.). Plasma and plasma ultrafiltrate were stored at -20°C until analysis. Urine samples were collected before cisplatin administration and then from 2-hour pools during a 24-hour period. The volume of urine for each collection period was recorded. Tissue samples were digested with a 4 mol/L concentration of nitric acid; after evaporation to near dryness the residue was dissolved in a 10 mmol/L concentration of nitric acid. Each sample was compared with appropriate standards to take the matrix effect into account. Platinum concentrations in plasma, plasma ultrafiltrate (free platinum), urine, and tissues were determined by flameless atomic absorption spectroscopy according to the technique described by Pera and Harder,¹³ with use of a Hitachi model Z-9000 polarized Zeeman spectrophotometer (W. Pabisch Instrument, Milan, Italy). The accuracy of platinum determinations was verified by neutron activation analysis, as previously described.¹⁴

Lung specimens for morphologic evaluation of parenchymal damage were obtained before drug infusion and at the completion of treatment. Samples were divided into two halves. The first half was prefixed (1 hour) in Bouin's solution and used for light microscopy investigations. The second half was fixed in 2.5% glutaraldehyde solution and used for scanning (SEM) and transmission electron microscopy (TEM) examinations.

The area under the concentration $\times$ time curve (AUC) from 0 to 60 minutes was estimated by the trapezoidal rule. The indices of platinum exposure were the observed plasma platinum concentrations and the AUC values. Repeated-measures analysis of variance was used to assess changes with time of the investigated lung function parameters.

Results

After 60-minute lung perfusion, the volume of the circuit priming fluid was increased by 50% (700 ml); this was most likely caused by bronchial flow emptying into the pulmonary circulation. The overall procedure was completed in every case, and no complications occurred during the operation (mean duration, 220 minutes). There were no intraoperative or postoperative deaths. The only postoperative complication (2 cases) was the development, 48 hours after treatment, of radiologic signs of interstitial and alveolar edema, depicting the previously described "contusion syndrome"¹⁵ (Fig. 2). In one case, prolonged (5 days) respiratory support was needed, whereas the other patient recovered after 2 days of standard medical therapy. The mean hospital stay was 11 days (range, 8 to 17 days). There was no late morbidity caused by the procedure. At a median follow-up of 13 months (range, 9 to 21 months), four patients are alive without any evidence of disease relapse. One patient died of extrapulmonary metastases 11 months after the operation. The remaining patient had both local and

Fig. 2. Chest roentgenogram, 48 hours after isolated lung perfusion, showing conspicuous interstitial and alveolar edema in treated organ.

distant disease relapse 9 months after treatment. Traditional chemotherapy toxicity, such as myelosuppression, nausea and vomiting, and alterations in creatinine, nitrogen, sodium, and potassium blood values, never occurred.

Platinum concentrations in the pulmonary and systemic plasma are reported in Fig. 3. The AUC (AUC: 0 to 60 minutes) values (milligrams/milliliter $\times$ minute) for total platinum concentrations in pulmonary and systemic plasma were 12.8 (SD,* 5.6) and 0.30 (SD, 0.2), respectively. Systemic plasma total platinum concentrations 6 and 12 hours after treatment were 0.25 $\mu\text{g/ml}$ (SD, 0.4) and 0.23 $\mu\text{g/ml}$ (SD, 0.4), respectively. Ultrafilterable platinum was never detectable in systemic plasma. These figures relate to the pulmonary-to-systemic crossover, which was very small. The half-life for total and ultrafilterable platinum in pulmonary plasma was 1.08 hours (SD, 0.6) and 0.89 hours (SD, 0.3), respectively. Total platinum concentrations in the normal lung parenchyma and metastatic tissue are illustrated in Fig. 4. At the completion of lung perfusion, total platinum concentration in mediastinal lymph nodes was 2.57 $\mu\text{g/gm}$ wet weight (SD, 1.47). The mean percentage of platinum excreted in the urine up to 24 hours after cisplatin administration was 0.88% (SD, 0.30%) of the administered platinum dose.

Changes of ventilatory function parameters are illustrated in Fig. 5. The analysis of variance showed

*Standard deviation.

Fig. 3. Semilogarithmic plot of total and filterable platinum (PT) concentrations versus time, in systemic and pulmonary plasma, during isolated lung perfusion (values represent means plus or minus standard deviation).

Fig. 4. Platinum (PT) concentrations in normal lung and neoplastic tissue during isolated lung perfusion (values represent means plus or minus standard deviation).

significant differences between preoperative values and those registered either 10 or 30 days after treatment (forced vital capacity [FVC]: $p < 0.001$; forced expiratory volume in 1 second [FEV₁]: $p < 0.02$; carbon monoxide diffusing capacity: $p = 0.02$). Ventilatory parameters were functionally reassessed in two patients 12 months after the procedure and showed a further improvement (13% reduction of both FVC and FEV₁ with respect to preoperative values). Postoperative lung scanning showed no evidence of ventilation/perfusion mismatch, although scattered defects of both ventilation and perfusion were seen. Histologic examination of normal lung parenchyma showed no damage as a result of the perfusion with platinum. TEM and SEM examinations evidenced the integrity of the alveolar septa and epithelial lining. Minimal cellular changes, such as mild pneumocyte hypertrophy with ectasia of the smooth endoplasmic reticulum were seen (Fig. 6).

Discussion

The reasons that support a multimodality approach for the treatment of lung metastases from soft tissue sarcomas have already been emphasized.¹⁶ The rational basis for use of regional chemotherapy rests on the concept that, in the metastatic cascade, there is a phase during which the disease is limited to the lung. This concept is supported by numerous findings: (1) the lung is the first district of metastatic spread in approximately 80% of sarcomas^{4, 5, 15, 17}; (2) pulmonary metastases are the primary cause of death in patients with sarcoma^{3, 18}; (3) even after a complete resection of pulmonary metastases, the major recurrence site remains the lung¹; and (4) many patients who die with pulmonary metastatic disease have no extrathoracic spread at autopsy.^{5, 19} The approach of combining surgical excision with regional chemotherapy has been previously used in patients with localized melanoma of the limbs and was found to offer the best chance for cure.²⁰ The present experience shows

Fig. 5. Changes of pulmonary function parameters before and after isolated lung perfusion. *DLCO*, diffusing capacity of carbon monoxide; *PO₂*, oxygen tension; *PCO₂*, carbon dioxide tension.

that such a combined approach may also be applied to the lung.

We used cisplatin, an antineoplastic agent, because (1) the drug had been used in our previous experimental study, with results that suggested acute lung damage would be low¹² and (2) platinum antitumor activity has been reported for a great variety of tumors, with the percentage of objective responses in adult soft tissue sarcomas being about 20%.^{7, 21} Because our previous experimental study suggested that the overall toxicity of the combined treatment was more related to the surgical trauma (including extracorporeal circulation) than to the drug dose, we planned a pilot study to investigate the feasibility of the procedure, instead of a phase I trial. We believed it would have been unethical to apply escalating doses of cisplatin, because patients treated with suboptimal drug doses would still undergo the surgical trauma and this would not be balanced by an adequate probability of treatment efficacy.

The outstanding clinical finding of this study is the demonstrated feasibility of a therapeutic program including metastasectomy and isolated lung perfusion with cisplatin. The overall procedure is safe and the operative risk and short- and long-term morbidity remained low. However, because interstitial and alveolar pulmonary edema may occur during the

postoperative period, an intensive care unit must be available.

Systemic side effects, both subjective and hematologic, as the result of antineoplastic drug administration were always absent. This finding possibly depends on the lack of significant platinum escape from the perfusion circuit to the general circulation. If we assume that side effects consequent to cisplatin administration are related to the concentrations of filterable platinum in plasma,^{22, 23} it is likely that the reduced systemic exposure to active platinum species, observed in patients undergoing lung perfusion with cisplatin, may account for the absence of systemic toxicity.

Rather than systemic platinum toxicity, lung tolerance of the drug is likely to be the limiting factor. No serious acute damage to the pulmonary parenchyma has morphologically been demonstrated. Either the epithelial alveolar lining or the capillary membrane was intact. This finding is in keeping with the experimental data obtained from our laboratory.¹² However, the interval between treatment and lung specimen removal was too short to draw final conclusions. Investigations to estimate long-term toxicity in animal models are ongoing. Changes of ventilatory function parameters after treatment were consistent with the reduction of lung volumes as a result of metastasectomy. The decrease of

Fig. 6. TEM and SEM appearances of normal pulmonary parenchyma after 1 hour of isolated lung perfusion. *Top left*, Intact interalveolar septum with minimal pneumocyte hypertrophy (TEM, original magnification $\times 4400$). *Top right*, Detail of interalveolar septum showing pneumocyte with mild ectasia of smooth endoplasmic reticulum (TEM, original magnification $\times 3000$). *Bottom left*, Undamaged capillary wall (TEM, original magnification $\times 4400$). *Bottom right*, Complete and uninjured alveolar epithelial lining (SEM, original magnification $\times 390$).

carbon monoxide diffusing capacity was also compatible with lung volume reduction, although permeability changes may not be excluded. Nevertheless, functional changes seemed to be reversible, as suggested by the progressive tendency to recovery. Lung damage during perfusion was avoided by maintenance of an appropriate osmolarity of the perfusate, high oxygen tensions in the circuit, an unobstructed pulmonary venous return, and flow rates to prevent high pulmonary artery pressure. However, the individual effects of the perfusate composition, platinum toxicity, and pulmonary circulation patterns on lung damage are difficult to separate.

According to the results of our previous experi-

mental study, the present clinical trial confirmed that great pharmacokinetic advantages are attained with the use of the isolated lung perfusion technique. It also demonstrated that no significant difference in drug extraction exists between normal lung and neoplastic tissue. The technique we have applied implies a number of points that could give rise to criticisms.

First, although isolated perfusion of both lungs has already been accomplished with use of two completely separate pumping circuits,^{11, 24} we adopted a lateral approach with single-lung exploration. Consequently, staged thoracotomy was required in patients with bilateral disease. Indeed, the use of a median sternotomy would make the proce-

cedure significantly harder and increase the risk of postoperative respiratory impairment, because of to the potential of a bilateral pulmonary contusion syndrome. Moreover, there is no general agreement on the best approach for the treatment of lung metastases.^{25, 26} Sequential operations at the time lesions become evident on computed tomographic scan have been reported to be as efficacious as early excision of occult tumors.²⁵ Residual posterior nodules have been found at a subsequent exploration in patients who had undergone resection through median sternotomy.¹⁸ We can state that staged lung perfusion through lateral thoracotomy is a safe procedure and would not result in tumor unresectability at the second operation.

Second, isolated lung perfusion is a single-course treatment, the effectiveness of which remains unknown. However, in patients already scheduled for metastasectomy, the procedure does not require extensive additional trauma and it may be followed by either conventional chemotherapy or different types of regional chemotherapy.

Third, the criteria that identify patients who will benefit from isolated lung perfusion remain unsettled. The prediction of a complete resection and the absence of disease outside the chest were the main criteria we adopted. Other indicators, including the number of metastases, the disease-free interval, and the tumor doubling time, were not taken into account, because there is no unanimity on their prognostic value.²⁶ In the present series, two patients with 6 and 14 nodules, respectively, underwent lung perfusion, although this finding has been associated with an unfavorable outcome.²⁷ The first patient is alive without any evidence of disease relapse 10 months after the operation, whereas the other patient died of extrapulmonary metastases 11 months after treatment.

Fourth, the use of the isolated lung perfusion technique assumes that pulmonary metastases are supplied by the pulmonary circulation and that the neoplastic tissue takes up antitumor drugs at a rate similar to that of lung tissue. The major blood supply to lung metastases through the pulmonary artery has been demonstrated by several investigations.^{28, 29} Our study showed that, during perfusion, lung and tumor are exposed to similar concentrations of platinum, at least when the metastasis diameter is smaller than 1 cm. Platinum concentrations in larger metastases were not investigated, because they were removed during the operation.

Fifth, the systemic-to-pulmonary crossover of

blood (representing the fraction of the bronchial flow that empties into the pulmonary circulation) added a dilutional volume to the pulmonary perfusion circuit, resulting in a decrease of platinum concentration in the perfusate greater than that caused by drug uptake. To avoid the progressive decrease of platinum concentrations in the perfusate, additional doses of the drug could be fractionally administered. This administration modality has already been tested in our animal model.¹²

In conclusion, this study demonstrated that normothermic isolated perfusion of a single lung with platinum can be accomplished without serious systemic toxicity or adverse clinical effects. Lung damage seems to be reversible to some degree. Because the perfusion system is a closed circuit, manipulations of the system conditions (hyperthermia)³⁰ or perfusate composition (tumor necrosis factor,³¹ anticancer drug association) could be done to enhance the treatment effectiveness.

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