Phase I Study of Inhaled Doxorubicin for Patients with Metastatic Tumors to the Lungs

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Abstract

Purpose: To evaluate the toxicity profile of inhalational doxorubicin in patients with malignant disease in the lung.

Experimental Design: The OncoMyst Model CDD-2a inhalation device aerosolizes compounds to particles of 2 to 3 μm and prevents exhaled aerosol from escaping into the environment. Deposition efficiency of inhaled Technetium 99m was used to predict deposition of doxorubicin and calculate dose. Treatment was repeated every 3 weeks. No more than moderate pulmonary dysfunction was permitted (forced expiratory volume in 1 s, forced vital capacity, and diffusing capacity for carbon monoxide, all >50% of predicted; resting SaO2 >90%).

Results: Fifty-three patients were enrolled at 13 dose levels ranging from 0.4 to 9.4 mg/m². The most common histologic diagnoses were sarcoma (n = 19) and non–small cell lung cancer (n = 16). Dose-limiting toxicity (DLT) was observed at the 9.4 mg/m² dose level when two of four patients experienced pulmonary DLT. Of 11 patients treated at the 7.5 mg/m² dose level, only one showed DLT consisting of a decline in forced vital capacity of >20% from baseline. No significant systemic drug-related toxicity was observed. Several patients experienced declines in pulmonary function test variables, which were attributed to progressive disease. Observed activity included a partial response in a patient with metastatic soft tissue sarcoma previously treated with i.v. doxorubicin and ifosfamide.

Conclusions: Inhaled doxorubicin is safe up to a dose of 7.5 mg/m² every 3 weeks in patients with cancer who had normal to moderately impaired pulmonary function.

Pulmonary metastases commonly occur in solid tumors and are often the predominant or sole site of metastatic involvement. A problem in treating these lesions is the inability to achieve adequate therapeutic concentrations of drugs at the tumor site without suffering substantial systemic toxicity. One approach to improving therapeutic efficacy is targeted dose intensification. This approach has been effectively used in a variety of tumors, including liver, ovarian, and bladder cancer (1–6), but there is little experience delivering chemotherapeutics directly to the lungs via inhalation (7).

Inhalational chemotherapy was first described by Shevchenko and Resnik in 1968. (8). The concept was tested in dogs and subsequently in 58 patients. Antitumor efficacy was observed in 24 patients, but the data are difficult to interpret because of the concurrent use of radiotherapy and less precise methods for response assessment. Tatsumura et al. (9) tested the administration of 5-fluorouracil by inhalation in dogs and found high levels of the drug in the trachea, bronchi, and regional nodes. Subsequently, the same authors treated 10 patients with inoperable lung tumors with 5-fluorouracil via a supersonic nebulizer at a dose of 250 mg twice daily for 2 to 3 days per week. There was notable antitumor efficacy, and the therapy was well tolerated. Similar proof-of-principle studies using inhaled doxorubicin or paclitaxel in dogs with macroscopic lung tumors showed preliminary evidence of activity with acceptable toxicity (10).

Huland et al. (11) administered interleukin-2 by inhalation with concomitant IFN-α given s.c. to 15 patients with metastatic renal carcinoma. There was a marked difference in response between lung and non-lung metastases (1 complete response and 8 partial response in lung metastases compared with 0 complete response and 3 partial response, in non-lung metastases), suggesting that inhalational interleukin-2 displayed enhanced antitumor efficacy in pulmonary lesions.
More recently, investigators have tested the feasibility of delivering liposomal interleukin-2 to patients with pulmonary metastases and found that they were able to deliver up to 6 million units of interleukin-2 thrice daily with no significant toxicity (12).

Based on these data, we investigated the feasibility of administering chemotherapeutic agents via inhalation. Preliminary studies in dogs and rodents had shown that it is possible to administer compounds with vesicant properties via this route without serious local or systemic toxicity. Evidence of antitumor efficacy had been observed in mice and in dogs with inhaled doxorubicin (13, 14). Doxorubicin was selected for clinical testing because of its broad spectrum of antitumor efficacy and showed feasibility in animals. One of the major issues associated with the use of doxorubicin i.v. is the potential for systemic short and long-term toxicity, including cardiac toxicity. We hypothesized that local delivery of an agent with significant activity and systemic toxicity would retain local (pulmonary) activity while limiting systemic toxicity. The incorporation of a technetium deposition test to determine the amount of deposited drug within the lungs is a unique aspect of this device and method of administration. Similarly, safeguards are built into the system to minimize the potential for ambient escape of aerosol.

We report here the results of a phase I study of doxorubicin given by inhalation to patients with primary or metastatic tumors affecting the lungs.

Patients and Methods

Study design and objectives. This was a phase I multicenter dose escalation study in patients with advanced cancer affecting the lungs. The principal objective was to establish the maximum tolerated dose of inhaled doxorubicin given every 3 weeks. We sought to define the nature of the toxic effects of inhaled doxorubicin and to evaluate its pharmacokinetic profile, in particular its systemic availability when given via this route. The dose of doxorubicin was specified as the number of deep breaths that the patient was to take and was individually determined based on the efficiency of Technetium 99m deposition before treatment.

Study population. Patients had cancer metastatic to the lung, age ≥18 years, and Karnofsky performance status ≥70%. In addition to adequate bone marrow, hepatic, and renal function, patients were required to have adequate pulmonary function: diffusing capacity for carbon monoxide, forced vital capacity, and forced expiratory volume in 1 s ≥50% predicted; resting oxygen saturation ≥90%; exercise oxygen saturation ≥85%.

No therapy for 3 weeks before entry was allowed, and patients must have recovered from the toxicity of prior therapy and could not have received any radiation therapy to the lungs. Chest wall or breast irradiation was allowed provided there was no pulmonary damage attributed to radiation therapy. Left ventricular ejection fraction at or above the lower limit of normal was required. Prior anthracycline use was allowed but could not be associated with cardiac toxicity or exceed a total cumulative dose of 450 mg/m².

Women could not be pregnant or breast-feeding; patients were required to use an effective contraceptive method during and for 6 months after completing therapy. Patients who had prior therapy with mitomycin (>25 mg/m²), bleomycin or nitrosoureas (>200 mg/m²), or with any pulmonary toxicity from prior chemotherapy were excluded. Similarly, patients with asthma, complete atelectasis, and pneumonectomy were excluded from participation. All patients provided informed consent.

Oncomyst model CDD-2a. The Oncomyst Model CDD-2a is a high-efficiency inhalation device that uses a Pari LC Plus nebulizer housed within a sealed containment system with apparatus for mouth-only inhalation. A microprocessor controls an air compressor to pulse the nebulizer for a predetermined time interval. The atomized drug (2-3 µm particle size) accumulates in a plenum chamber and is inhaled by the patient through deep inspiration. The device captures any fugitive aerosol. All exhaled air is filtered through a Pall HME 15/22 filter before exhausting. The drug nebulization component is discarded after a single use, and the containment box is decontaminated before reuse. A system for immediate shutdown in the event of device malfunction or patient distress is also incorporated.

Doxorubicin inhalation solution. Doxorubicin inhalation solution was an investigational, sterile, pyrogen-free solution supplied at concentrations (16 and 24 mg/mL) in 20% ethanol/80% water (pH 3).

Treatments. Doxorubicin inhalation was administered every 3 weeks. The dose was calculated based on the Technetium 99m deposition test and was expressed as the number of deep breaths for the patient to inhale. The Technetium 99m deposition test and scintigraphy were undertaken before the first treatment. The patient was instructed to breathe normally with the device for two to four breaths followed by a deep breath to full lung capacity with a 5-s breath hold. The deposition test was designed to determine the fraction of the inhaled aerosol that was deposited in the patient and to quantify the “blow-by” aerosol not available to the patient for inspiration. It consisted of a filter test and a post-filter test inhalation phase. By measuring the counts in the nebulizer before and after nebulization and by counting each of the filters, inhale, blow by, and exhale, the fraction of nebulized Technetium 99m retained in the patient is calculated. This is the “deposition efficiency.”

The doxorubicin inhalation took place with the patient inside a demister tent with a HEPA filter. The therapist activated the solenoid – 2 s before deep inspiration. This breathing pattern was maintained until the calculated number of deep breaths was completed. Upon completion of the inhalation, the patient rinsed his/her mouth with water and washed his/her face. The patient was observed for 30 min after completion of the procedure.

Selection of doses in the study. The starting dose was 0.4 mg/m², approximately one tenth the maximum tolerated dose in dogs. This was escalated to 0.6, 0.8, and 1.2 mg/m². Subsequent dose levels were increased at 25% increments until 9.4 mg/m². If any patient at a dose level experienced dose-limiting toxicity (DLT), the dose level was to be expanded to six patients. If two of the first six or fewer patients had DLT, dose escalation stopped. A minimum of three patients were accrued and completed one course without DLT before escalation to the next dose level could proceed. The maximum tolerated dose was defined as the dose level at which fewer than two of six patients experienced DLT.

Dose delays/adjustments. DLT was defined as any of the following: any grade 4 hematologic toxicity or neutropenic fever, any grade 3 nonhematologic toxicity using the National Cancer Institute Common Toxicity Criteria version 2.0, radiographic evidence of interstitial disease with symptoms (grade 2 Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Lung Late Radiation Morbidity Scoring Scheme), resting SaO₂ of <88% before the next dose, decrease from baseline in diffusing capacity for carbon monoxide, forced expiratory volume in 1 s, or forced vital capacity ≥20% before the next dose. Only the first course was considered for the purposes of dose escalation; however, pulmonary DLT occurring in any course was reason for removal from the study.

Pharmacokinetics. The protocol called for a single measurement of doxorubicin and doxorubicinol to be collected within 5 min (Cmax) following completion of the first course of treatment until the dose was escalated to a level at which the Cmax for doxorubicin was at least 10 ng/mL, a concentration considered to be sufficiently high enough for reliable pharmacokinetic measurements. Therefore, a more complete plasma pharmacokinetic profile was generated by collecting blood
Results

Demographic and other baseline characteristics. Fifty-three patients were enrolled in the study. Three patients were enrolled twice, once at a low dose level for three cycles then subsequently (after 3 months of stability) at a higher dose level (Table 1).

Study courses. Thirteen dose levels were evaluated ranging from 0.4 to 9.4 mg/m² inhaled doxorubicin per course. Before the initiation of the 3.8 mg/m² dose level, the maximum number of courses a patient could receive at a given dose level was 3, although patients could reenter at a higher dose level if criteria for reentry were met. Subsequently, the protocol was amended to permit patients to receive six courses of therapy and a further amendment allowed for an unrestricted number of courses.

Adverse events. Table 2 includes patients with grade ≥3 adverse events as well as all pulmonary events. The majority of study-related adverse events were pulmonary. The most frequent pulmonary adverse event was increased cough in 27 patients (26 grade 1-2). In addition, other grade 1 or 2 pulmonary events included dyspnea (n = 9), chest pain (n = 5), wheezing (n = 4), hoarseness (n = 3), hemoptyis (n = 1), and bronchospasm (n = 1). There were five severe (grade 3-4) pulmonary adverse events. One patient had grade 3 hypoxia at the 3.8 mg/m² dose level. One patient at the 7.5 mg/m² dose level had a >20% drop in forced vital capacity deemed to be drug related, and this cohort was expanded to six patients with no additional DLTS. At the 9.4 mg/m² dose level, two of four patients entered at this dose level had severe toxicities, including one patient who experienced respiratory distress and a second patient who developed bilateral ground glass infiltrates that were consistent with drug effect. Subsequently, an additional five patients were treated at the 7.5 mg/m² dose level without additional DLT. For five patients who had a decrement in their pulmonary function test results following one to five cycles of treatment, the treating physician interpreted these changes as being due to progressive disease in the lungs and not to drug.

As shown in Fig. 1, whereas there was some decrement in particular patients in forced vital capacity, forced expiratory volume in 1 s, or diffusing capacity for carbon monoxide (either due to DLT or progressive disease), for most patients, pulmonary function test variables remained relatively stable. For diffusing capacity for carbon monoxide, there was a transient decline in the first one to two courses in some cases, but unless it reached the level of DLT, this measure most often recovered over time.

Table 1. Patient characteristics

| Age | Median (range) | 54 (24-76) |
|dropdown| Karnofsky performance status | 90-100 | 38 |
| | 80 | 15 |
| | 70 | 0 |
| Primary diagnoses | Sarcoma | 19 |
| | Lung | 16 |
| | Colorectal | 6 |
| | Osteosarcoma | 4 |
| | Thyroid | 3 |
| Miscellaneous* | 5 |
| Baseline pulmonary function tests (% predicted) | FVC 50-75/>75 | 14/39 |
| | FEV1 50-75/>75 | 21/32 |
| | DLCO 50-75/>75 | 16/37 |

*One each from mesothelioma, hepatocellular carcinoma, retinoblastoma, endometrial carcinoma, and unknown primary.

Table 2. Severe (grade 3) adverse events and all pulmonary toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Adverse reaction</th>
<th>No. patients / courses (dose for severe, mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Respiratory distress/dyspnea</td>
<td>1/1 (9.4)</td>
</tr>
<tr>
<td>3</td>
<td>Hypoxia</td>
<td>1/1 (3.8)</td>
</tr>
<tr>
<td>3</td>
<td>Chemotoxic reaction</td>
<td>1/1 (9.4)</td>
</tr>
<tr>
<td>3</td>
<td>Cough</td>
<td>1/1 (9.4)</td>
</tr>
<tr>
<td>2</td>
<td>Cough</td>
<td>3/12</td>
</tr>
<tr>
<td>2</td>
<td>Wheezing</td>
<td>1/1</td>
</tr>
<tr>
<td>1</td>
<td>Wheezing</td>
<td>3/12</td>
</tr>
<tr>
<td>1</td>
<td>Dyspnea</td>
<td>4/5</td>
</tr>
<tr>
<td>1</td>
<td>Dyspnea</td>
<td>5/6</td>
</tr>
<tr>
<td>1</td>
<td>Pain in chest</td>
<td>5/6</td>
</tr>
<tr>
<td>1</td>
<td>Hoarseness</td>
<td>3/3</td>
</tr>
<tr>
<td>1</td>
<td>Hemoptyis</td>
<td>1/1</td>
</tr>
<tr>
<td>1</td>
<td>Bronchospasm</td>
<td>1/5</td>
</tr>
</tbody>
</table>

NOTE: Other grade 3 adverse events not related to the study drugs include hip and spine pain, diarrhea, decline in performance status, hypotension, cellulitis, and broken ankle.
One patient died on study. The patient was a 50-year-old male, with bronchoalveolar carcinoma involving both lungs, who received his first dose of inhaled doxorubicin at the 9.4 mg/m² dose level. He experienced severe shortness of breath with an oxygen saturation of 50%, was admitted, and provided ventilatory support. The patient's condition continued to deteriorate; ventilatory support was withdrawn and he died. At autopsy, the lungs were extensively involved by mucinous bronchoalveolar carcinoma and also exhibited acute obstructive pneumonia, predominantly in the right lower lobe. The tumor involved the pleura and extended into the larger airways with evidence of local tumor necrosis. Focal hyaline membrane deposition was noted. The postmortem lung culture was negative, although lung blood cultures were positive for coagulase-negative Staphylococcus and for Acinetobacter baumannii. The cause of death was felt to be acute obstructive pneumonia secondary to extensive tumor load and tumor extending into the larger airways.

Non-pulmonary toxicities were mild (grade 1-2) and transient. The most common non-pulmonary toxicities were sore throat (10), anorexia (8), taste disturbance (7), fatigue (6), nausea (5), sore tongue/mouth (4), tachycardia (3), and dyspepsia (2). One each had the following grade one toxicities: increased salivation, transient increase in blood pressure, alopecia, rash, metallic odor in perspiration, reversible eosinophilia, and decrease in left ventricular ejection fraction. This patient's left ventricular ejection fraction declined from 53% at baseline to 45% at off-study evaluation and was considered possibly study-related by the investigator. The patient did not, however, suffer symptomatic congestive heart failure. There was no evidence of myelosuppression in any of the courses given. In addition, no consistent changes were observed in chemistry values. One patient experienced transient, asymptomatic increase in alanine aminotransferase from baseline, to a maximum of 113 units/L, which returned to normal after receiving 16 courses of treatment (6 at 1.9 mg/m² and 10 at 6.0 mg/m²). No patient had significant mucositis, or effect on nutritional status, and there was no evidence of hematologic toxicity.

**Pharmacokinetic summary.** The results of the doxorubicin and doxorubicinol assays for course 1 indicated that at doses <3.0 mg/m², the C_max of doxorubicin never exceeded 10 ng/mL. At doses of 3.8 to 7.5 mg/m², the mean C_max and AUC(0-6) of doxorubicin were linear and dose dependent, increasing 1.7 and 1.6 times, respectively, as the dose increased 2-fold over this range (Fig. 2; Table 3). In contrast, increasing the dose from 7.5 to 9.4 mg/m², a dose increase of 25%, resulted in more than a doubling of the C_max and AUC(0-6). The C_max of doxorubicin following inhalation of doxorubicin at doses ranging from 0.4 to 9.4 mg/m² was dose dependent and never exceeded 7 ng/mL. These concentrations are considerably below those reported following i.v. administration of doxorubicin.

The C_max was observed at the first sampling point (5 min). This is consistent with the delivery of the agent and predicted lipophilicity of doxorubicin. At higher doses, the time of administration approached 45 min; therefore, the level observed 5 min after completing treatment may have been more steady state (although time points during inhalation were not done in this study).

**Antitumor activity.** One partial response was documented in this study in a patient with spindle cell sarcoma. The response was initially seen at a dose level of 1.9 mg/m² with six cycles of treatment. The patient maintained this response and was reentered at the 6.0 mg/m² dose level. She received 10 additional courses of treatment before being withdrawn from the study still in response.

Stable disease lasting ≥5 courses (range, 5-15) was reported in eight patients: two with bronchoalveolar carcinoma, two with soft tissue sarcoma, one with endometrial carcinoma, and three with thyroid cancer. Six patients had stable disease through three courses but were withdrawn because the protocol was originally limited to three courses. Two patients were withdrawn after one course without documentation of progressive disease, and the remaining patients experienced disease progression as their best response.

**Discussion**

This is the first study to evaluate the safety of doxorubicin given by the inhalation route. The rationale for this route of
administration was to deliver therapy targeted to the sites of disease, thus minimizing systemic toxicity. The study showed that inhaled doxorubicin can be administered safely, although pulmonary toxicity is dose limiting. The observed pulmonary toxicity at higher doses (7.5 and 9.4 mg/m²) suggests that, at least for this drug in this route, dose escalation will not be feasible. For most patients at the maximum tolerated dose (7.5 mg/m²) and below, the changes seen in pulmonary function test variables were within the limits set by the study (i.e., 20% change in pre-study treatment). However, at least five patients were noted to have decrement in their pulmonary function test variables coinciding with progressive disease. For these patients, the changes were interpreted by the investigator as being due to progressive disease and not from drug. As noted above, several patients had <20% decrement in their diffusing capacity for carbon monoxide during the first few cycles of treatment, which then reversed with further treatment.

The limited pharmacokinetic profile that we obtained with inhalational doxorubicin is consistent with the observed minimal systemic toxicity. The maximal observed plasma concentration of doxorubicin was 47.8 ng/mL, well below concentrations observed after i.v. bolus administration. Greene et al. did a pharmacokinetic study of doxorubicin in 10 patients with i.v. bolus administration of 75 mg/m² (15). These investigators found there to be a biphasic elimination of doxorubicin, with an initial C_max of nearly 2,000 ng/mL. Even after 1 h, in the terminal phase of elimination, the average concentration was nearly 45 ng/mL (15). With prolonged continuous low-dose i.v. administration (~3.9 mg/m²/d), the steady-state/maximum plasma concentrations were close to that seen with inhalation therapy (averaging 6 ng/mL; ref. 16). Our maximal concentrations were noted at the initial time point (5 min). As noted above, as the dose increased, number of breaths and deliver time approached 45 to 60 min. Even if delivery were instantaneous, one would predict that peak doxorubicin delivery/absorption would occur rather quickly (17). Schanker et al. had determined that the absorption of small molecules through an inhalation route is determined more by lipophilicity than by size. Doxorubicin would be predicted to be a relatively hydrophobic/lipophilic drug (18) with absorption from the lungs in the range of minutes as was seen. These low concentrations are consistent with the apparent lack of systemic toxicity associated with inhaled doxorubicin.

Although locally delivered therapy has theoretical advantages (i.e., enhanced local delivery of active drug with minimal systemic delivery/toxicity), there are only a few situations where locally directed therapy has achieved widespread use. Local therapies for noninvasive bladder cancer (19), brain tumors (20, 21), and most recently stage III ovarian cancer (6) have shown improved local control and, in some settings, improved survival.

Is there a place for local administration of therapy for patients with lung cancer? Three potential strategies can be envisioned: incorporation of inhalational therapy for patients with advanced disease, incorporation of inhalational therapy into adjuvant strategies, and use of inhalational compounds for chemoprevention.

Table 3. Pharmacokinetic summary

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dose (no. patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.8 (5)</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>11.6 ± 8.0</td>
</tr>
<tr>
<td>AUC(0-6 h) (ng/mL h)</td>
<td>23.2 ± 10.9</td>
</tr>
</tbody>
</table>
The addition of the anti–vascular endothelial growth factor monoclonal antibody bevacizumab to chemotherapy in select patients was recently reported to improve survival when compared with chemotherapy alone (22). Until recently, the addition of a third agent to standard “doublet” therapy for the treatment of advanced non–small cell lung cancer has proved disappointing. Furthermore, the addition of a third cytotoxic agent to platinum-based therapy has been difficult because of overlapping toxicities of the chemotherapy. It is possible that for patients in whom bevacizumab is not an option (which may be the majority of patients with advanced non–small cell lung cancer), the addition of an agent such as inhaled doxorubicin may hold promise.

Should such a study show promise, then one might speculate that the addition of inhaled doxorubicin to adjuvant therapy would be reasonable and testable (23, 24). This strategy of inhaled “adjuvant” doxorubicin also may ultimately apply to other surgically treated diseases with frequent recurrence/metastasis to the lungs, such as sarcomas and thyroid cancer. A final potential application of inhalational approaches is that of chemoprevention. Two required preconditions for effective chemoprevention are an effective agent and minimal or no toxicity. Inhalational approaches present an attractive option for minimizing toxicity.

Limitations to this approach are evident in the inclusion and exclusion criteria for this initial study. Specifically, patients must have no more than moderate pulmonary dysfunction, cannot be oxygen dependent, and cannot have received prior radiation therapy to the chest. In addition, patients who have had a prior pneumonectomy were excluded from this study. These qualifications limit the applicability of this strategy to patients with lung cancer until additional studies show the safety of treating patients with these characteristics.

The major limitation of expanding upon this experience in patients with lung metastases is the potential and fear of pulmonary toxicity as was seen in three patients in this study at the highest doses. Several interpretations are possible. One could argue that pulmonary toxicity is unacceptable and will not allow for further treatment, particularly in patients with advanced non–small cell lung cancer who are the most logical patients for such treatment. The data based upon this phase I trial is that only 1 of 11 patients treated at the recommended phase II dose of 7.5 mg/m² developed significant pulmonary toxicity (drop in forced vital capacity). Before this conclusion could be verified, additional patients should be treated. A different interpretation might be that this agent is too toxic, but that other inhalational agents might offer more hope. Although there is not much data with alternative agents using the OncoMyst device, preliminary animal data may lend support to this interpretation. In the pilot study in dogs, both paclitaxel and doxorubicin were administered via a similar device designed for endotracheal instillation in dogs (10). With limited numbers of subjects, pulmonary toxicity was not observed with paclitaxel, whereas changes consistent with pneumonitis or fibrosis were observed in some dogs receiving doxorubicin. This was manifest by intermittent, nonproductive cough within 1 to 10 days of therapy. In addition, whereas radiographic findings of pneumonitis was absent in the doxorubicin treated dogs, there was some evidence of pulmonary toxicity on histologic sections at necropsy (10). Again, the data in this study are not dramatic at the phase II dose, and in addition, whereas the canine data raise some concern, there certainly may be species differences in the toxicity profile of this agent. Finally, one could interpret these data as showing a reasonable safety profile, but that further testing of this agent (either by itself or, more likely, in combination with systemic therapy) should be done with careful attention to pulmonary function tests.

Further study of inhaled doxorubicin in combination with i.v. chemotherapy to test the hypothesis that increased therapeutic intensity to the lungs may reduce lung relapse and morbidity associated with tumors in the lungs is warranted, particularly for patients without prior lung disease.

Acknowledgments

We thank Larry Schauf, Ph.D for the helpful insights.

References


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