Computed Tomography Assessment of Lung Density in Patients With Lung Cancer Treated With Accelerated Hypofractionated Radio-Chemotherapy Supported With Amifostine

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Objectives: Lung fibrosis is a severe complication after radiotherapy in patients with nonsmall cell lung cancer and is the main undesirable late complication limiting the therapeutic ratio of thoracic radiation treatment. Here we evaluated the lung fibrosis using computed tomography scan mediated assessment of lung tissue density in long-term survivals treated with hypofractionated and accelerated radiotherapy supported with amifostine (HypoARC).

Methods: Out of 45 patients with locally advanced nonsmall cell lung cancer treated with conformal HypoARC (3.5 Gy × 15 fractions in 4 weeks) and concurrent chemotherapy, 14 are alive 16 to 47 months (median 20) after radiotherapy. Patients received 500 to 1000 mg of amifostine before each radiotherapy fraction, according to a previously described dose individualization algorithm.

Results: Early pneumonitis was absent in all patients, whereas lung density assessed with computed tomography scan in Hounsfield units (HU), within a median of 20 months after radiotherapy, showed marked increase in 2/6 and 0/8 patients who received 500 to 750 mg and 1000 mg of amifostine, respectively. The HU in these 2 patients increased to values below −550 HU, from initial values of −700 to −800 HU. Only one of these 2 patients had mild exertional dyspnoea.

Conclusions: Given the good tolerance of daily high-dose amifostine administration and the encouraging very low rates of pneumonitis and lung fibrosis noted, despite the aggressiveness of the radio-chemotherapy regimen applied, it is suggested that the value of amifostine in chest radiotherapy should be re-evaluated in properly designed randomized clinical trials.

Key Words: radiotherapy, lung fibrosis, amifostine

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Concurrent radio-chemotherapy is the gold standard for the treatment of inoperable non metastatic nonsmall cell lung carcinoma (NSCLC).[1] The dose of radiotherapy (RT) strongly defines the local control and survival of these patients.[2–4] Higher dose, however, goes along with higher rate of radiation pulmonary fibrosis (RPF), the main undesirable late complication limiting the therapeutic ratio of radiation treatment.[5] Although modern RT techniques, such as conformal RT or intensity-modulated RT allow dose escalation by limiting the normal tissue complication probability, RPF remains a major concern and research on methods that would further reduce the incidence of this complication is warranted to ameliorate the survival rates and the quality of life of NSCLC patients.

Research on amifostine, a wide spectrum cytoprotective agent,[6] resulted in conflicting results as far as protection against RPF is concerned. Randomized studies by Antonadou et al showed significant protection against early and late radiation lung injury[7,8] and similar results were obtained by Komaki et al in a series of patients with NSCLCs treated with cisplatin/etoposide radio-chemoterapy with or without amifostine.[9] In a more recent randomized study, however, amifostine failed to reduce the incidence of RPF in NSCLC patients undergoing hyperfractionated radiotherapy with weekly paclitaxel and carboplatin chemotherapy.[10] In this later study, amifostine was used 4 times per week and before the second daily fraction, which may have compromised the cytoprotective efficacy.[11]

Indeed, in experimental studies the cytoprotective effect of amifostine is dose dependent[12] so that higher amifostine dose may be necessary to substantiate a clinical benefit, especially when applying aggressive regimens such as taxane-based radio-chemotherapy. The dose of 200 to 300 mg/m^2 used in the clinical routine is arbitrary. In a dose individualization trial performed by our group, about 80% of patients can safely receive a subcutaneous daily dose of amifostine between 750 to 1000 mg,[13] and such higher dose may unmask the clinical benefits amifostine can offer.

In 2 consecutive protocols we assessed the feasibility of an aggressive hypofractionated and accelerated regimen combined with chemotherapy supported with a daily high-dose amifostine.[14,15] Here we evaluated the long-term pulmonary lung injury using computed tomography (CT) scan mediated assessment of lung tissue density in long-term survivals recruited in these trials.

MATERIALS AND METHODS

Forty-five patients with locally advanced inoperable NSCLC were treated with hypofractionated accelerated radio-chemotherapy supported with cytoprotection (chemo-HypoARC). In a first protocol,[14] 31 patients received concurrent chemotherapy with liposomal doxorubicin (Caelyx, 25 mg/m^2) and oxaliplatin (Eloxatin, 50 mg/m^2), every 2 weeks. In a subsequent protocol,[15] 14 patients received pegylated liposomal doxorubicin (Caelyx) at a standard dose of 20 mg/m^2 every 2 weeks and Vinorelbine (Navelibine) was administered orally a dose of 20 to 30 mg/m^2 thrice every 2 weeks. Patient and disease characteristics of 14/45 cases assessed with CT scan for lung fibrosis are shown in Table 1.

Radiotherapy was delivered using a 3D-conformal technique based on CT imaging, using a 6–18 MV LINAC. The same technique was used in both chemotherapy protocols. The gross tumor volume (GTV) was defined as the tumor volume apparent by CT imaging and endobronchial extension as shown by bronchoscopy. All lymph nodes larger than 1 cm in CT scans were included in the GTV. The clinical target volume was defined as GTV plus a 0.5-cm margin within pulmonary parenchyma and the whole nodal station of lymph nodes considered as pathologic. The planning treatment volume consisted of a 1-cm margin to the respective clinical target volumes. Dose homogeneity criteria within planning treatment volumes had to be within 95% to 107% of the prescribed dose. A new planning was performed 7 days after the 10th fraction to better define treatment volumes, expected to have changed because of

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TABLE 1. Characteristics of Patients Assessed With CT for Lung Fibrosis

Total no. patients	14
Male:female	14:0
Age, yr	
Median	66
Range	46–76
WHO PS	
Median	1
Range	0–2
Tumor type	
Squamous cell	11
Adenocarcinoma	1
Undifferentiated	2
AJCC TNM stage	
T2,3–N3–M0	8
T4–any N–M0	5
T4–N1–M1*	1
Previous treatment	
Chemotherapy naïve	6
Pretreated	8
% LV80†	
Mean ± SD	28.4 ± 5.0
Range	23.6–36.9
95% CI	25.5–31.0

*Adrenal metastasis.
†Percentage of the lung volume that received ≥80% of the tumor dose.

tumor shrinkage. Patients received 15 fractions of 3.5 Gy within 4 consecutive weeks (1 week split after the 10th fraction), which corresponds to a radiobiologic equivalent of 65.6 Gy (α/β ratio for lung parenchyma = 4). Given the more than 2-week abbreviation of the overall treatment time, the biologic dose to the tumor is estimated to be higher than 70 Gy. Detailed radiobiological analysis had been previously reported.[14]

Twenty minutes before each fraction of radiotherapy, patients received 500 to 1000 mg of amifostine (Ethyol), depending upon tolerance, diluted in 5 mL of water for injection, injected in 2 divided doses of 500 mg (2.5 mL) to the right and left arms subcutaneously. Tropisetron was given per os, 1 hour before amifostine injection, to prevent emesis. The dose of 1000 mg was reached gradually (first day 500 mg, second day 750 mg, and third day 1000 mg) using a previously published algorithm allowing the individualization of the dose of amifostine.[13]

After therapy, patients entered a follow-up protocol including physical examination, standard blood/serum test, and thoracic/abdominal CT scan once every 2 months for the first 6 months, and once every 3 months thereafter. Fourteen out of 45 (31%) are alive 16 to 47 months after therapy and changes in the lung tissue density were analyzed in these patients.

CT Scan Lung Fibrosis Evaluation

CT scan of the whole chest area before radiotherapy and 16 to 47 months after RT (median, 20 months) was available in 14 patients (11/31 treated in the oxalipaltin/liposomal doxorubicin study and 3/14 treated in the vinorelbin study). Three chest CT sections, 1 at the central level of the main tumor mass and 1cm above and below this level were chosen. Regions of interest, comprising the whole lung avoiding the tumor (1-cm margin) were drawn in the irradiated and controlateral lungs, before and after RT (Fig. 1). The mean

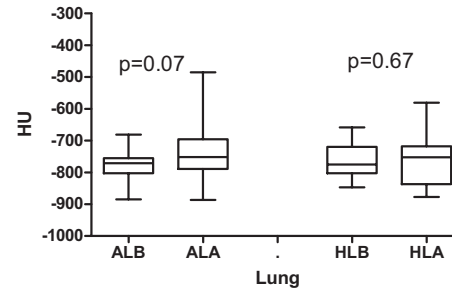

FIGURE 1. Lung tissue density presented as CT scan HU in the affected/tumor bearing (AL) and healthy (HL) lungs, before (B) and after (A) a median of 20-month period from radiotherapy.

density and standard deviation within these areas was calculated using the logismic of the CT apparatus. Density was counted in Hounsfield units (HU) representing the mean attenuation of the tissue examined, in a scale where "0" represents the water and "−1000" the air density.

The statistical analysis and graph presentation was performed using the GraphPad Prism 5.0 version package. The paired 2-tailed *t* test was used for testing differences between categorical variables. *P* values <0.05 were considered for significance.

RESULTS

Using the amifostine individualization protocol,[13] 18/45 (40%) patients received a daily amifostine dose of 1000 mg, 12/45 (26.7%) of 750 mg, and 6/45 (13.3%) of 500 mg. At this individualized dose levels, only mild nausea or fatigue was occasionally reported by patients. Five out of 45 (11%) patients interrupted amifostine because of fever/rash symptomatology and 4/45 (8.8%) did not tolerate the dose of 500 mg (intolerable nausea/vomiting and/or fatigue), so amifostine was interrupted. Detailed analysis of amifostine tolerance has been previously reported.[14,15]

Using the dose volume histograms we calculated that the percentage of the lung that received ≥80% of the tumor dose was 28.4% (range, 23.6–36.9; standard deviation, 5.0). Radiologic and/or clinical evidence of early radiation pneumonitis (during and up to 2 months after the end of radiotherapy) was absent in all 45 patents recruited in the 2 clinical trials. Out of 14 patients available for long-term lung toxicity evaluation, 8 received 1000 mg, 4 received 750 mg, and 2 received 500 mg of amifostine daily before each radiotherapy fraction.

Figure 1 shows the radiation pulmonary fibrosis in terms of lung tissue CT density (HU) of the affected and healthy lung, before and after radio-chemotherapy supported with amifostine. The mean lung density of the nonaffected lung remained stable. This was −768 ± 51 versus −763 ± 77 before and after radiotherapy, respectively (P = 0.67). On the contrary, lung density was increased in the affected lung. The mean density was −774 ± 48 versus −725 ± 120 before and after radiotherapy, respectively. This difference approached significance (P = 0.07). Figure 2 shows CT images with regions of interest drawn (before and after radiotherapy) in 2 patients; 1 with evident and 1 with absence of lung fibrosis.

This increase of the lung tissue density in the affected (irradiated) lung was mainly because of the marked fibrosis noted in 2 patients. This is shown in Figure 3. In these 2 patients the lung density increased above −550 HU, from initial values of −700 to −800 HU. A third patient also showed high HU after radiotherapy but the individual lung tissue (affected and healthy) density of this patient was already quite high even before RT. From a clinical point

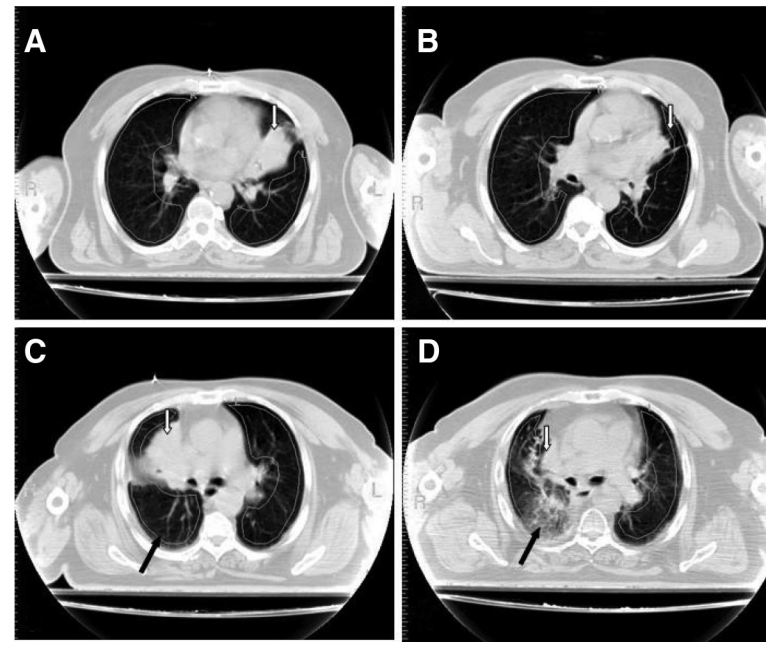

FIGURE 2. CT scans with regions of interest drawn within the lungs for the assessment of lung tissue density. Figures 1A, B, corresponding to CT images before (A) and 47 months after (B) radiotherapy, show lack of pulmonary fibrosis. Figures 1C, D, corresponding to CT images before (C) and 20 months after (D) radiotherapy, show marked lung fibrosis (black arrows). Both patients are in complete response (white arrows show the tumors in A and C and a remnant fibrotic area after radiotherapy in B and D).

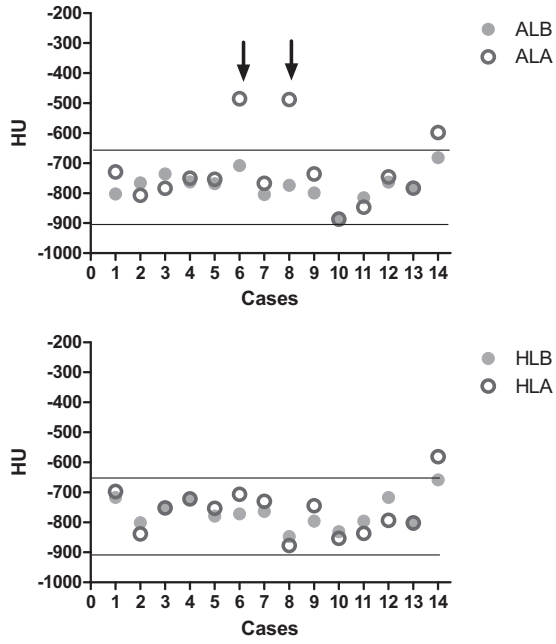

FIGURE 3. Scatter-gram of lung tissue density presented as CT scan HU in the affected/tumor bearing (AL) and healthy (HL) lungs, before (B) and after (A) a median of 20-month period from radiotherapy. Noted the marked increase of lung tissue density of the affected lung in only 2 out of the 14 evaluated patients (arrows).

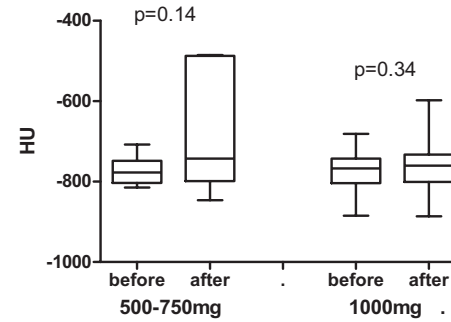

FIGURE 4. Lung tissue density presented as CT scan HU of the affected/tumor bearing lung before and after a median of 20-month period from radiotherapy, according to the daily dose of amifostine.

of view mild exertional dyspnoea was evident in 1 of these 2 patients with increased lung tissue density, although no medical support was necessary.

Analysis of the HU before and after radiotherapy in 2 groups of patients according to the daily dose of amifostine delivered (500–750 mg vs. 1000 mg) showed that the lung tissue density was clearly altered only in the lower dose group, although the difference did not reach significance ($P = 0.14$; Fig. 4).

DISCUSSION

Lung fibrosis is a major side-effect of radiotherapy that compromises the quality of life of patients with lung cancer.[16] The incidence of this complication seems to sharply increase at doses higher than 64 Gy (given with standard fractionation), so that many centers are reluctant to offer higher doses to patients. As the local control chances are directly linked to the dose of radiotherapy,[2–5] any policy that can reduce the incidence of this severe complication would eventually allow the safe administration of higher biologically active dose to the chest and, presumably, better local control and survival. Such policies would be also important in the feasibility of aggressive radio-chemotherapy protocols that, although associated with high response rates, bear higher in-field toxicity.[17,18]

Aside to conformal and intensity-modulated RT technology, chemical cytoprotection with amifostine introduced in the mid nineties in the clinical practice sustained the optimism that radiotherapy could become less toxic and, eventually, more potent

through dose escalation protocols. Although amifostine clearly reduced the incidence of xerostomia, its efficacy on the prevention of mucositis or of late radiation sequelae such as lung fibrosis remains controversial.[7–10] The arbitrary low dose schedule of amifostine applied in all randomized trials performed may have masked the expected benefits. In the large randomized study by Movsas et al,[10] the incidence of grade 3 to 4 lung fibrosis was 9% and 12% in the group of amifostine and in the control group, respectively. Amifostine was given at low dose (500 mg i.v.) before the afternoon fraction of the hyperfractionated radiotherapy regimen, for 4 days per week, so that cytoportection was allowed for only 40% of the total number of fractions. Moreover, the higher toxicity rate expected from the inclusion of a taxane in the radio-chemotherapy regimen,[19] further reduced the eventual impact of the already low amifostine dose in protecting against the regimen. A higher total subcutaneous amifostine dose could have shown better protection efficacy, with the tolerance profile of amifostine being maintained at the same levels. Indeed, in a dose individualization study we showed that 8/10 patients can receive a double daily dose of amifostine with excellent tolerance,[13] which is 5 to 6 times higher than the dose delivered in the Movsas et al study.[10] This dose individualization protocol of amifostine was applied in 2 studies in NSCLC patients receiving a highly aggressive accelerated and hypofractionated regimen combined with chemotherapy, showing a low rate of acute radiation toxicity.[14,15]

In this study, we evaluated the incidence of late radiation lung fibrosis in 14 patients who survived 16 to 47 months after therapy. CT images could provide a more detailed assessment of lung tissue damage even in cases without clinical symptomatology. Although an overall substantial increase of lung tissue density of the irradiated lung was noted, this was a result of prominent fibrosis noted in 2/14 patients. Only 1 of these had mild exertional dyspnoea. Analysis according to the amifostine dose showed that these patients were treated at the 500 to 750 mg dose level, whereas none of the patients treated at the 1000 mg dose showed increase of the lung tissue density.

Overall, the lung tolerance (early and late) was excellent despite the aggressiveness of the radio-chemotherapy regimen and this should be attributed to the protective effect of amifostine aside to the conformal techniques applied. Given the good tolerance of a daily high-dose amifostine administration and the encouraging very low rates of pneumonitis and lung fibrosis noted in our phase II trials, the value of amifostine in chest radiotherapy should be re-evaluated in properly designed randomized clinical trials.

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