Hypofractionated Accelerated Radiochemotherapy with Cytoprotection (Chemo-HypoARC) for Inoperable Non-small Cell Lung Carcinoma

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Abstract. *Background: Concurrent radiochemotherapy and altered radiotherapy fractionation are under thorough investigation in locally advanced non-small cell lung carcinoma (NSCLC). Patients and Methods: The efficacy and tolerance of hypofractionated accelerated radiochemotherapy supported with high dose (up to 1000 mg daily) amifostine cytoprotection (hypoARC) was examined in 31 patients. Fifteen fractions of 3.5 Gy were delivered within 28-35 days. Liposomal doxorubicin and oxaliplatin were concurrently given. Results: A total of 65% of patients tolerated a daily amifostine dose of 750-1000 mg. Chemotherapy had an excellent tolerance. Grade 3 oesophagitis was noted in 7/31 (22.5%) patients. Radiation pneumonitis was absent and radiation fibrosis minimal. Complete and partial response were observed in 12/31 (38.6%) and 17/31 (54.8%) patients, respectively. The 2-year estimated local progression-free and overall survival interval were 58% and 45%, respectively. Conclusion: Given the simplicity of HypoARC, the very low morbidity, and the high complete response and survival rates obtained, HypoARC regimens deserve further testing.*

Concurrent radiochemotherapy followed by chemotherapy is considered the standard therapy for locally advanced non-small cell lung carcinoma (NSCLC) (1). Although platinum compounds are widely used for combination with radiation, novel agents such as taxanes, gemcitabine or liposomal doxorubicin have shown remarkable complete response rates, at the cost of increased toxicity (2).

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The radiation dose is an important factor influencing the outcome of radiotherapy (3), but no definitive guidelines exist regarding the fractionation of radiotherapy. Hyperfractionated techniques *e.g.* Radiation Therapy Oncology Group (RTOG) studies (4), aim to deliver a high radiotherapy dose to the tumor while maintaining a relatively low biological dose to the lungs, as indeed predicted by the low α/β values for lung tissues. On the other hand, accelerated radiotherapy schemes *e.g.* continuous hyperfractionated accelerated radiotherapy CHART trial (5) bear improved efficacy despite the rather low total tumor dose. Such schemes aim to abolish the adverse effect of rapid tumor repopulation on the radiotherapy efficacy by squeezing the overall treatment time. Indeed, a daily dose of up to 0.8 Gy is consumed after the 3rd week of radiotherapy to compensate for the rapid repopulation phenomenon (6).

RTOG and CHART studies use small fractions per dose to avoid acute pneumonitis and subsequent fibrosis. Nevertheless, NSCLC is often hypoxic also sharing an increased intrinsic radioresistance, so that low α/β values are likely to characterize a large percentage of these tumors. Moreover, acceleration of radiotherapy, although able to abrogate the rapid clonogen repopulation, minimizes any advantage that could be gained by the re-oxygenation effect expected during longer courses of radiotherapy. As shown in a recent study in head and neck cancer, low-dose fractions are not effective in hypoxic tumors despite acceleration (7). Large fractions of radiotherapy may be more effective, at least in cases with poor oxygenation and/or low intrinsic radiosensitivity. Especially when rapid repopulation ability co-exists, high dose accelerated hypofractionated radiotherapy may prove superior. Such schemes, however, may induce severe early and late esophageal/lung toxicity.

In the present study, a hypofractionated accelerated radiotherapy scheme combined with concurrent

chemotherapy with novel agents (liposomal doxorubicin and oxaliplatin) was tested in patients with inoperable non-small cell lung cancer. Conformal techniques and high dose daily amifostine were used to minimize the risk of severe pneumonitis and lung fibrosis.

Patients and Methods

Recruitment criteria. Thirty-one patients with locally advanced inoperable NSCLC (stage IIIb/IV) were treated with hypofractionated accelerated radiochemotherapy supported with cytoprotection (chemo-HypoARC). One of these patients had brain metastasis at diagnosis (treated also with radiotherapy) and one had adrenal metastasis. Nine patients had progressive disease during chemotherapy and 22 were chemotherapy naive. Patients' PS ranged from 0 to 2 (median 1). Table I shows the patient characteristics. The follow-up of patients ranged from 3-32 months (median 16). One patient was lost to follow-up at 4 months. At the time of analysis, 17 patients were alive (follow-up 16-32 months, median 25).

The Chemo-HypoARC regimen to study lung tolerance and treatment efficacy has been approved by the local trial committee and written informed consent was obtained from all patients.

Table I. *Patient characteristics.*

Total no. of patients	31
Male:Female	29:2
Age (years)	
Median	65
Range	43-76
WHO performance score	
Median	1
Range	0-2
Tumor type	
Squamous cell	26
Adenocarcinoma	3
Undifferentiated	2
TNM stage	
IIIb	29
IV	2
Prior treatment	
Chemotherapy naive	22
Taxane-containing	9
Platinum-containing	7
Gemcitabine-containing	3

Pretreatment and treatment evaluation. Baseline studies included physical examination, whole blood count WBC, complete biochemical profile, bone scan and CT of the chest and upper abdomen. Patients were followed with WBC, serum urea and creatinine and liver enzymes once every two weeks during the radiotherapy/chemotherapy period. Acute radiation toxicity was registered daily and radiotherapy delay was enforced in case of acute pneumonitis, grade 3 esophagitis, or grade 3 hematological toxicity. The National Cancer Institute (NCI) Common Toxicity Criteria Version 2 scale was used to assess chemotherapy and acute radiation toxicity. The RTOG toxicity scale was used to assess late radiation sequel (RTOG and NCI Toxicity Criteria: www.accessdata.fda.gov/scripts/cder/onctools/toxicity.cfm)

Response to treatment was assessed with a CT scan on day 21 (to allow modification of the radiotherapy fields), every 2 months for the first 6 months and every 3 months thereafter.

Radiotherapy schedule. Radiotherapy treatment planning was based on CT-simulation and 3D-conformal definition of radiotherapy portals. The primary tumor and part of the mediastinum were included to deliver a daily dose of 3.5 Gy (5 fractions per week) to a total 'physical' dose of 35 Gy (44 Gy in 12 days, calculated for $\alpha/\beta=4$ Gy). After a 9-day split, new planning was performed targeting the radiologically detectable disease. An additional 5 fractions of 3.5 Gy were delivered. The total physical dose to the tumor was 52.5 Gy (65.6 Gy in 26 days, for $\alpha/\beta=4$ Gy). The 'biological' dose (normalized total dose, NTD) is calculated using a previously proposed formula: $NTD = D\ [(\alpha/\beta + d)/(\alpha/\beta + 2)]$, where D is the total physical dose and d is the dose per fraction (8).

The time-corrected biological dose ($NTD_{(T)}$) was calculated as: $NTD_{(T)}= D\ [(\alpha/\beta + d)/(\alpha/\beta + 2)] + \lambda(T_c-T_o)$, where T_c is the number of days required for the delivery of the NTD using a conventionally fractionated scheme, T_o is the number of days required for the delivery of the accelerated scheme, and λ is the estimated daily dose consumed to compensate for rapid tumor repopulation (8). The overall treatment time of 26 days is reduced by 19 days compared to a standard radiotherapy scheme that would deliver an equal biological dose of 65.6 Gy. Assuming a time factor 'λ' of 0.4-0.8 Gy/day (estimated in a previous study (6)), the time-corrected biological radiation dose to the tumor ranges from 73-80 Gy. For the normal lung, a λ of 0.2 Gy predicts for a maximum dose to certain lung areas proximal the tumor of 73 Gy. For patients who accomplished therapy with one week delay (36 days), the acceleration is 12 days, so the biological time-corrected dose for these patients is still high, ranging from 70.4-75.2 Gy.

Amifostine administration. Twenty minutes before each fraction of radiotherapy, patients received 1000 mg of amifostine (Ethyol®), diluted in 5 ml of water for injection, injected in two 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 higher dose of amifostine (1000 mg instead 500 mg) applied in the protocol was chosen in order to better protect tissues against the large fractions of radiotherapy in the HypoARC scheme.

The dose of 1000 mg was reached gradually (1st day 500 mg, 2nd day 750 mg and 3rd day 1000 mg) using a previously published algorithm (9). The tolerance of amifostine was recorded daily using a scoring system (9). According to this scale the tolerance of amifostine was scored as good/acceptable, poor, or unacceptable for each dose level. If at any point of therapy patients showed poor tolerance (grade 3/4 nausea/emesis or grade 3/4 fatigue), dexamethasone 8 mg was administered intramuscularly immediately before injection of amifostine and tolerance was re-assessed the day after. If good tolerance was confirmed amifostine was continued as prescribed. If not, the dose was reduced to 750 mg and, if necessary, to 500 mg. If patients did not tolerate the dose of 500 mg well, amifostine was interrupted. No more than 2 dexamethasone injections were allowed per week of radiotherapy, otherwise the dose of amifostine was reduced. Amifostine-related

Table II. *Mean dose of amifostine received by patients according to the performance score.*

	All cases	Performance score 0-1
Mean dose (mg)	No. of pts. (%)	No. of pts. (%)
<500*	7 (22.6)	3 (12)
<500**	2 (6.5)	2 (8)
500-700	2 (6.5)	1 (4)
750-850	8 (25.7)	7 (28)
900-1000	12 (38.7)	12 (48)
Total	31	25

*Due to emesis / fatigue; **due to fever/rash.

Table III. *The grade of esophagitis experienced by patients according to the mean dose of amifostine received.*

Oesophagitis	Grade			
Amifostine dose level	0-1	2	3	4
Amifostine dose level				
Low (<500 mg)	0	5	4	0
Medium (500-850 mg)	1	6	3	0
High (900-1000 mg)	7	5	0	0
Total	8	16	7	0

P-value=0.009 (Chi-square two-tailed *t*-test).

fever/rash or necrolytic syndrome attributed to amifostine (or to any other drug) was followed by immediate interruption of amifostine and oral administration of cortisone and antihistamines for 3 days (10).

Chemotherapy. Chemotherapy started on the first day of radiotherapy using a combination of liposomal doxorubicin (Caelyx® 25 mg/m^2; dose established in a previous study (11)) and oxaliplatin (Eloxatin® 50 mg/m^2; chosen due to reduced emesis/fatigue and easy administration compared to cisplatin), every 2 weeks. Patients were supported with haematopoietic growth factors as appropriate. Chemotherapy continued for four consecutive months (8 cycles).

Statistical analysis. The statistical analysis and graphic presentation of survival curves was performed using the GraphPad Prism 4.0 version package. The Chi-square and two-tailed *t*-test were used for testing differences between categorical variables. Survival curves were plotted using the method of Kaplan and Meier. A *p*-value of <0.05 was considered statistically significant.

Results

Amifostine tolerance. Table II shows the dose of amifostine administered to patients. Overall, 65% of patients received a daily dose of 750-1000 mg. The administration of this dose level was feasible in 76% of patients with good (0-1) performance status. Emesis and fatigue were the reasons for reduction of the mean dose of amifostine to levels 500-700 mg in 2 patients and to levels lower than 500 mg in 7 patients. Two additional patients interrupted amifostine due to fever/rash symptomatology (4-5th injection). In both cases, fever regressed within 2 hours using paracetamol and the rash regressed within 2-3 days following oral cortisone and antihistamine therapy. Skin erythema around the site of injection was noted in 6/31 patients.

Chemotherapy toxicity. None of the patients presented with neutropenia higher than grade 1. No platelet or hemoglobin toxicity was noted. No palmar/plantar erythrodysesthesia or out-portal mucositis was noted during the course of radiotherapy. This type of grade 2 toxicity, however, appeared in 10/31 patients after the 4th or 5th chemotherapy cycle, and a one week delay was enough to obtain regression and treatment continuation and completion without further delays.

In-field toxicity. Esophagitis was the main acute in-field toxicity noted (Table III). Grade 2 esophagitis was noted in 16/31 (51%) and grade 3 in 7/31 (22.5%) patients. This, however, was significantly less severe ($p=0.009$) in patients treated at the 900-1000 mg dose level of amifostine. Radiation induced acute pneumonitis was not noted in any of the patients. Skin toxicity grade 2 (focal moist skin desquamation) was noted in 3/31 patients treated at the low/medium amifostine dose level.

Symptomatic lung fibrosis grade 2 (persistent cough and dyspnea with minimal effort) was noted in 1/9 patient and long lasting thoracic wall pain grade 2 appeared in another 1/9 patients treated at the <500 mg amifostine dose level. Limited grade 1, asymptomatic, fibrosis at the area of maximum dose (tumor area) was the worse toxicity documented in CT scans in patients treated at dose levels >500 mg.

Treatment time. Documentation of grade 3 esophagitis in 7 patients was followed by a delay in administration of the 3rd chemotherapy cycle and of the last 5 radiotherapy fractions, till regression to grade 1. In 4/7 patients, regression was obtained in 7 days so the treatment was accomplished in 32 days. For the remaining 3/7 patients the treatment was accomplished in 35-40 days.

A one-week delay of administration of this last radiotherapy phase (but not of chemotherapy) was also considered in an additional 10/24 patients experienced grade 2 esophagitis for various reasons (prevention of further deterioration of an initially poor PS, personal desire of some patients to rest for a longer period, physician's decision based on the expectation of further tumor shrinkage that would allow better shielding of normal

Table IV. *Overall treatment time in 31 patients.*

	Overall treatment time Days		
Amifostine dose level	26	32	>34
Amifostine dose level			
Low (<500 mg)	2	5	2
Medium (500-850 mg)	3	6	1
High (900-1000 mg)	9	3	0
Total	14	14	3

Table *p*-value=0.08 (Chi-square two-tailed *t*-test) (low/medium *vs*. high: *p*-value=0.02).

structures on the new treatment planning). In any case, one week's delay resulted in minimal loss of biologically active dose due to the intense acceleration of the scheme (see Patients and Methods). Overall, 12/31(38.7%) patients accomplished therapy within 26 days, 14/31 (45%) in 32 days and 3/31 (9.6%) patients in 35-40 days.

Table IV shows the overall treatment time according to the amifostine dose, showing a significant shorter overall treatment time in patients treated at the 900-1000 mg amifostine dose level.

Response and survival. Complete response of the chest tumor was observed in 12/31 (38.6%) patients and partial response in 17/31 (54.8%). The overall response rate was 93.5%. Minimal response or stable disease was observed in 2/31 (6.4%) patients. No differences could be detected among amifostine dose level groups or treatment time groups. The maximum shrinkage of the tumor was noted within 2-4 months from radiation. In 3 patients, delayed shrinkage was noted starting 2 months after radiotherapy completion, continuing up to 6-9 months and reaching complete response in 2 of these and a partial response in one.

The Kaplan-Meier local relapse-free survival (LRFS) and overall survival (OS) curves are shown in Figure 1. The one-year and 2-year estimated LRFS was 64% and 58%, respectively (median not reached). The OS at 1 and 2 years was 63% and 45%, respectively (median not reached). Out of 13 deaths that have occurred, 2 were related to local relapse (no evidence of metastasis), 8 to distant metastasis (no evidence of local disease progression) and 3 to both local and distant relapse.

Discussion

Non-accelerated hypofractionated radiotherapy has been applied in the past in several cancer centers for the treatment of locally advanced non-small cell lung cancer (NSCLC). Baillet *et al.* reported a series of 266 patients and showed that hypofractionation provides similar results to standard radiotherapy (12). In a large study on 301 patients, 24 Gy in 3 fractions or 30 Gy in 6 fractions provided results similar to standard radiotherapy in stage IIIb, with 1- and 2-year survival of 30% and 9%, respectively (13).

Acceleration of the hypofractionated regimen may improve the biological dose to the tumor (6). The administration of low total dose accelerated hypofractionated radiotherapy, using 2 fractions of 8-8.5 Gy one week apart has been applied in several institutes (14-18). The NTD for $\alpha/\beta=4$ Gy is around 36 Gy in one week, equivalent to 45-50 Gy if time factors are considered. Although excellent symptomatic relief is achieved with minimal toxicity, the median survival with this scheme ranges from 6-8 months (18).

Higher total doses using accelerated hypofractionation have been tried in some recent reports. Cheung *et al.* applied 12 consecutive fractions of 4 Gy (64 Gy biological dose calculated for $\alpha/\beta=4$ Gy, reaching 72-80 Gy time-corrected biological dose) in 33 patients, obtaining a 2-year survival of 46%. Subcutaneous fibrosis, however, was noted in 24% of patients (19). Using conformal radiotherapy, Thirion *et al.* administered 72 Gy with 3 Gy daily fractions (84 Gy biological dose calculated for $\alpha/\beta=4$ Gy) in 25 patients with stage I-III NSCLC. Long-term toxicity from lung and esoghagus was low and the 1-year survival was 68% (20). Lester *et al.* administered 15-20 consecutive fractions of 3.3-2.75 Gy in 135 NSCLC patients with stage I-III disease, obtaining a 44% 2-year survival without any severe late toxicity (21).

The combination of chemotherapy with hypofractionated radiotherapy has been less thoroughly examined. Cisplatin/5-fluorouracil administered with hypofractionated radiotherapy (3 Gy fractions) resulted in 53% and 16% overall survival for 1 and 2 years, respectively (22). Combination of protracted hypofractionated radiotherapy (5 Gy/week for 10 weeks; 75 Gy biological dose) together with weekly docetaxel resulted in 5% complete responses and 68% partial responses (23). An attempt to combine weekly paclitaxel and carboplatin with 20 consecutive fractions of 3Gy of radiation (70 Gy of biological dose in 4 weeks) failed due to important toxicity including tracheo-broncheal fistula formation and severe pneumonitis (24).

In the present study we applied a hypofractionated accelerated radiotherapy scheme in patients with inoperable NSCLC, combined with oxaliplatin and liposomal doxorubicin. Oxaliplatin, a potent platinum radiosensitizer (25, 26), was chosen due to its better tolerance profile (reduced emesis, renal and hematological toxicity) and to its easy administration compared to cisplatin. Our previous experience with liposomal doxorubicin showed selective accumulation in the tumor area and a good tolerance when combined with thoracic radiation, resulting in 21% complete response rates (11). Using docetaxel and liposomal doxorubicin with standard radiotherapy supported with

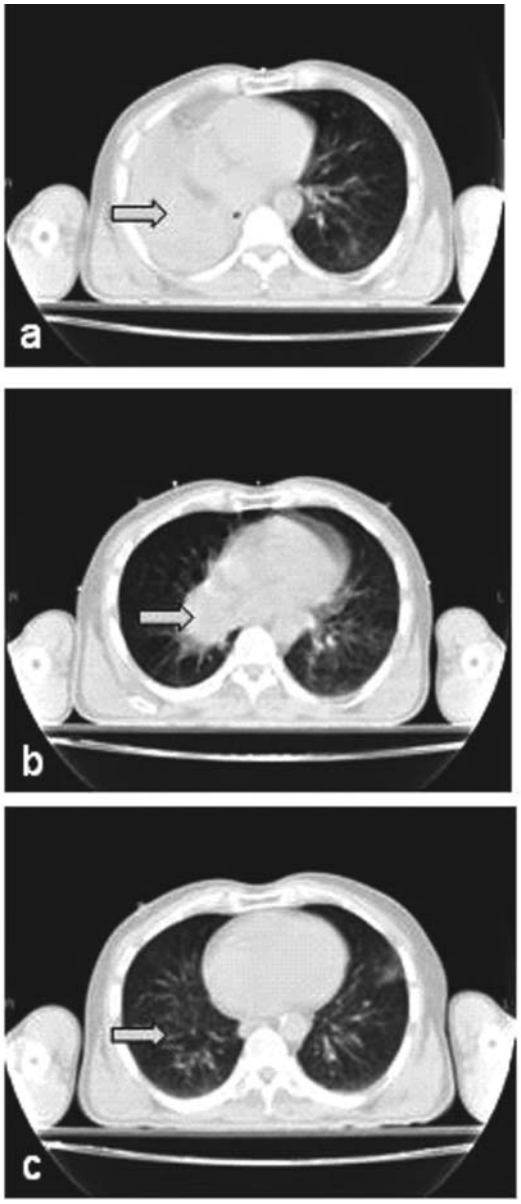

Figure 1. *A patient with squamous cell carcinoma with complete atelectasia of the right lung (arrow, a). Resolution of atelectasia after 5 fractions of 3.5 Gy reveals a tumor of the right main bronchus (arrow, b). Twenty-five months after therapy the patient is alive with no evidence of disease and no signs of radiation-induced lung fibrosis (arrow, c).*

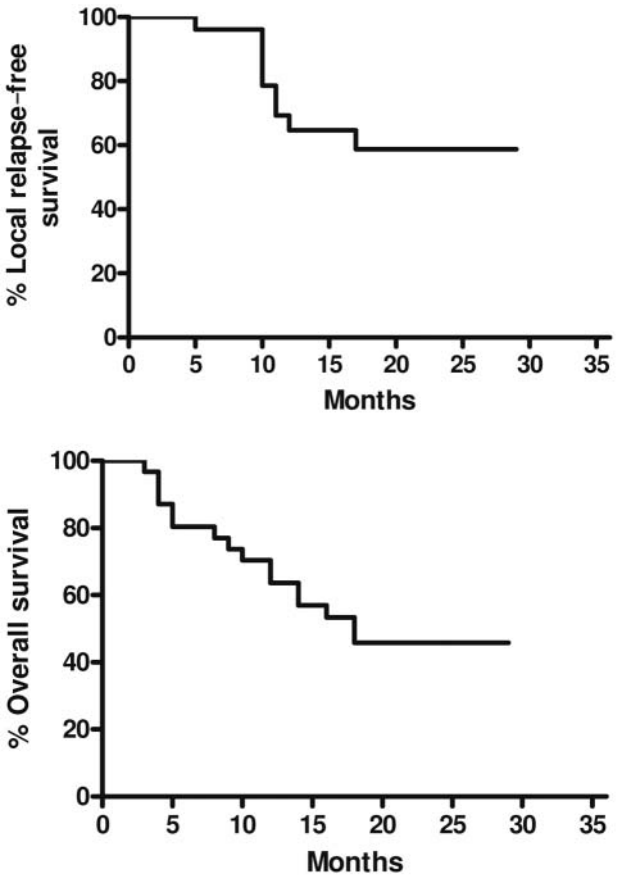

Figure 2. *Kaplan-Meier curves of A, local relapse-free and B, overall survival for 31 patients with stage IIIb/IV non-small cell lung carcinoma treated with hypofractionated accelerated radiotherapy supported with amifostine concurrently with liposomal doxorubicin and oxaliplatin.*

amifostine, we documented a 37% complete response rate with minimal toxicity (27).

Using the scheme herein reported, in-field radiochemotherapy toxicity was low with esophagitis grade 3 occurring in 7/31 (22.5%) of patients, resulting in prolonged radiotherapy delay (more than 1 week) in only 3/31 patients (9.6%). In 12/31 (38.7%) patients, where the amifostine dose was 900-1000 mg/day, no grade 3 esophagitis was noted and delays were significantly lower. Overall, the tolerance of amifostine was excellent in patients with good performance status (0-1), where 48% of patients tolerated a mean daily subcutaneous dose of 900-1000 mg and 28% a dose of 750-850 mg. This shows that up to a 2-fold higher daily dose of amifostine than that used to date (200-350 mg/m^2) can be well tolerated by the majority of patients with good performance status, which is probably important to obtain optimal cytoprotection. Experimental data show an important relation between the dose of amifostine and its cytoprotective efficacy, which may be critical when aggressive radiotherapy schemes, such as HypoARC, are applied (28).

Regarding acute pneumonitis, this was absent and symptomatic lung fibrosis was noted in just 1/7 (14%) patients treated at the <500 mg amifostine dose level. This very low incidence of lung fibrosis is impressive as the median follow-up of 17 alive patients is sufficiently long to have allowed appearance of late sequelae (median 25 months, range 16-32 months).

The current regimen delivered a biological dose of 65.6 Gy ($\alpha/\beta=4$ Gy), within 26 days (acceleration by 19 days). The time-corrected biological dose was 76-80 Gy and this was given together with chemotherapy. The 26-day treatment time was feasible for 14/31 patients, while for another 14/31 patients a short protraction by 5-7 days was necessary. In this way administration of a high time-corrected biological dose was feasible in 28/31 patients. Complete response was obtained in 12/31 (38.6%) patients and partial response in 54.8%, which compares favorably with our previous experience using standard radiotherapy with liposomal doxorubicine-based chemotherapy (11, 27). The 63% and 45% 1- and 2-year survivals obtained with HypoARC are promising.

An excellent tolerance profile regarding the out-field toxicity was noted, which was absent during the radiotherapy period. This suggests that further escalation of the oxaliplatin dose to levels higher than 50 mg/m^2 could be tested. The HypoARC itself followed by 3-month chemotherapy with liposomal doxorubicin and oxaliplatin at the prescribed dose was also adequate to provide a distant disease-free interval comparable to that expected from other adjuvant therapies. A total of 11/31 patients died with distant metastasis within a median follow-up of 14 months. One patient with adrenal metastasis and one with brain metastasis at diagnosis survived 22 and 14 months respectively without distant disease progression.

Given the simplicity of the hypofractionated accelerated radiotherapy scheme supported with amifostine–HypoARC (15 fractions *vs.* 36-50 fractions of the standard or hyperfractionated regimens), the very low acute and late morbidity of the scheme (25 months median follow-up for 17 alive patients), the excellent tolerance to chemotherapeutic drugs applied during HypoARC and the very high complete response and short-term survival rates obtained, it is concluded that this type of radiochemotherapy regimen deserves testing in large-scale randomized trials. Whether further radiotherapy dose escalation is feasible should be also investigated.

References

1 Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S Jr, Olak J, Stove, D, Strawn JR, Turrisi AT and Somerfield MR; American Society of Clinical Oncology: American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol *22*: 330-353, 2004.

2 Curran WJ: New chemotherapeutic agents: update of major chemoradiation trials in solid tumors. Oncology *63(Suppl 2)*: 29-38, 2002.

3 Trodella L, D'Angelillo RM, Ramella S, Ciresa M and Massaccesi M: Dose fractionation and biological optimization in lung cancer. Rays *29*: 319-326, 2004.

4 Movsas B, Scott C, Langer C, Werner-Wasik M, Nicolaou N, Komaki R, Machtay M, Smith C, Axelrod R, Sarna L, Wasserman T and Byhardt R: Randomized trial of amifostine in locally advanced non-small cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: radiation therapy oncology group trial 98-01. J Clin Oncol *23*: 2145-2154, 2005.

5 Saunders MI, Rojas A, Lyn BE, Pigott K, Powell M, Goodchild K, Hoskin PJ, Phillips H and Verma N: Experience with dose escalation using CHARTWEL (continuous hyperfractionated accelerated radiotherapy weekend less) in non-small cell lung cancer. Br J Cancer *78*: 1323-1328, 1998.

6 Koukourakis M, Hlouverakis G, Kosma L, Skarlatos J, Damilakis J, Giatromanolaki A and Yannakakis D: The impact of overall treatment time on the results of radiotherapy for nonsmall cell lung carcinoma. Int J Radiat Oncol Biol Phys *34*: 315-322, 1996.

7 Koukourakis MI, Bentzen SM, Giatromanolaki A, Wilson GD, Daley FM, Saunders MI, Dische S, Sivridis E and Harris AL: endogenous markers of two separate hypoxia response pathways (hypoxia inducible factor 2 alpha and carbonic anhydrase 9) are associated with radiotherapy failure in head and neck cancer patients recruited in the CHART randomized trial. J Clin Oncol *24*: 727-735, 2006.

8 Macejewski B, Taylor JM and Wither HR: Alpha/beta and the importance of the size of dose per fraction for late complications in the supraglottic larynx. Radiother Oncol *7*: 323-326, 1986.

9 Koukourakis MI, Abatzoglou I, Sivridis L, Tsarkatsi M and Delidou H: Individualization of the subcutaneous amifostine dose during hypofractionated/accelerated radiotherapy. Anticancer Res *26*: 2437-2443, 2006.

10 Boccia R, Anne PR, Bourhis J, Brizel D, Daly C, Holloway N 3rd, Hymes S, Koukourakis M, Kozloff M, Turner M and Wasserman T: Assessment and management of cutaneous reactions with amifostine administration: findings of the ethyol (amifostine) cutaneous treatment advisory panel (ECTAP). Int J Radiat Oncol Biol Phys *60*: 302-309, 2004.

11 Koukourakis MI, Koukouraki S, Giatromanolaki A, Archimandritis SC, Skarlatos J, Beroukas K, Bizakis JG, Retalis G, Karkavitsas N and Helidonis ES: Liposomal doxorubicin and conventionally fractionated radiotherapy in the treatment of locally advanced non-small-cell lung cancer and head and neck cancer. J Clin Oncol *17*: 3512-3521, 1999.

12 Baillet F, Maulard C, Dessard-Diana B, Manoux D, Housset M, Alapetite C, Michel-Langlet P and Delanian S: Curative radiotherapy of unresectable bronchial cancer. Apropos of 266 cases without metastasis with 4 to 6 years follow-up (oat cell carcinoma excluded). Ann Med Interne (Paris) *140*: 353-355, 1989.

13 Slotman BJ, Njo KH, de Jonge A, Meijer OW and Karim AB: Hypofractionated radiation therapy in unresectable stage III non-small cell lung cancer. Cancer *72*: 1885-1893, 1993.

14 Stevens MJ and Begbie SD: Hypofractionated irradiation for inoperable non-small cell lung cancer. Australas Radiol *39*: 265-270, 1995.

15 Devereux S, Hatton MQ and Macbeth FR: Immediate side effects of large fraction radiotherapy. Clin Oncol (R Coll Radiol) *9*: 96-99, 1997.

16 Plataniotis GA, Kouvaris JR, Dardoufas C, Kouloulias V, Theofanopoulou MA and Vlahos L: A short radiotherapy course for locally advanced non-small cell lung cancer (NSCLC): effective palliation and patients' convenience. Lung Cancer *35*: 203-207, 2002.

17 Cross CK, Berman S, Buswell L, Johnson B and Baldini EH: Prospective study of palliative hypofractionated radiotherapy (8.5 Gy x 2) for patients with symptomatic non-small-cell lung cancer. Int J Radiat Oncol Biol Phys *58*: 1098-1105, 2004.

18 Sundstrom S, Bremnes R, Aasebo U, Aamdal S, Hatlevoll R, Brunsvig P, Johannessen DC, Klepp O, Fayers PM and Kaasa S: Hypofractionated palliative radiotherapy (17 Gy per two fractions) in advanced non-small-cell lung carcinoma is comparable to standard fractionation for symptom control and survival: a national phase III trial. J Clin Oncol *22*: 801-810, 2004.

19 Cheung PC, Yeung LT, Basrur V, Ung YC, Balogh J and Danjoux CE: Accelerated hypofractionation for early-stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys *54*: 1014-1023, 2002.

20 Thirion P, Holmberg O, Collins CD, O'Shea C, Moriarty M, Pomeroy M, O'Sullivan C, Buckney S and Armstrong J: Escalated dose for non-small-cell lung cancer with accelerated hypofractionated three-dimensional conformal radiation therapy. Radiother Oncol *71*: 163-166, 2004.

21 Lester JF, Macbeth FR, Brewster AE, Court JB and Iqbal N: CT-planned accelerated hypofractionated radiotherapy in the radical treatment of non-small cell lung cancer. Lung Cancer *45*: 237-242, 2004.

22 Nagy-Mignotte H, Bolla M, Wuyam B, Blanc-Jouvan F, Moro D, Brambilla C, Paramelle B, Vincent F, Kolodie H and Vrousos C: Sequential combination of 5-fluorouracil, *cis*-platinum and irradiation in unresectable non-small cell lung cancer. Radiother Oncol *15*: 333-339, 1989.

23 Schwarzenberger P, Theodossiou C, Barron S, Diethelm L, Boyle M, Harrison L, Wynn RB, Salazar OM and Fariss A: Dose escalation of docetaxel concomitant with hypofractionated, once weekly chest radiotherapy for non-small-cell lung cancer: a phase I study. Am J Clin Oncol *27*: 395-399, 2004.

24 Machtay M, Washam C and Devine P: Pilot study of accelerated radiotherapy with concurrent chemotherapy for stage III non-small cell lung cancer. Semin Oncol *32*: S9-12, 2005.

25 Kjellstrom J, Kjellen E and Johnsson A: *In vitro* radiosensitization by oxaliplatin and 5-fluorouracil in a human colon cancer cell line. Acta Oncol *44*: 687-693, 2005.

26 Cappuzzo F, Novello S, De Marinis F, Franciosi V, Maur M, Ceribelli A, Lorusso V, Barbieri F, Castaldini L, Crucitta E, Marini L, Bartolini S, Scagliotti GV and Crino L: Phase II study of gemcitabine plus oxaliplatin as first-line chemotherapy for advanced non-small-cell lung cancer. Br J Cancer *93*: 29-34, 2005.

27 Koukourakis MI, Romanidis K, Froudarakis M, Kyrgias G, Koukourakis GV, Retalis G and Bahlitzanakis N: Concurrent administration of docetaxel and stealth liposomal doxorubicin with radiotherapy in non-small cell lung cancer: excellent tolerance using subcutaneous amifostine for cytoprotection. Br J Cancer *87*: 385-392, 2002.

28 Cassatt DR, Fazenbaker CA, Kifle G and Bachy CM: Effects of dose and schedule on the efficacy of ethyol: preclinical studies. Semin Oncol *30(Suppl)*: S31-39, 2003.

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