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ORIGINAL ARTICLE

Randomized phase II study of induction chemotherapy with gemcitabine plus cisplatin followed by sequential radiotherapy versus radiotherapy alone in patients with stage III non-small cell lung cancer

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Summary

Purpose: *This randomized phase II trial was conducted to compare the overall response rate (ORR) of gemcitabine plus cisplatin combination followed by sequential radiotherapy (RT) (arm A) versus RT alone (arm B) in chemonaïve patients with stage IIIA or IIIB non-small cell lung cancer (NSCLC). Secondary objectives were to evaluate time to progressive disease (TTPD), overall survival, and treatment tolerability in both arms.*

Patients and methods: *Eligible patients were required to have stage IIIA or stage IIIB NSCLC, no previous chemotherapy, ECOG performance status of 0-2, bidimensionally measurable disease, and age 18 to 75 years. Patients randomized in arm A were given 3 cycles of induction chemotherapy with gemcitabine 1250 mg/m^2 on days 1 and 8, plus cisplatin 80 mg/m^2 on day 1, every 21 days, followed by RT. In both arms, total dosage of RT was 63 Gy given in 34 fractions. Treatment continued until disease progression or unacceptable toxicity.*

Results: *Enrolled patients in both arms (30 in each arm) were well balanced for demographics and disease characteristics. The ORR, median TTPD and overall survival duration were 46.6/26.6%, 9.9/7.1 months and 12.5/10.0 months for arm A and arm B, respectively. The chemoradiation arm (arm A) was associated with significantly higher hematologic toxicities (anemia, neutropenia and thrombocytopenia) and nonhematologic toxicities (nausea, vomiting, paresthesias and alopecia).*

Conclusion: *Sequential chemoradiation seems to be more effective than radiation alone, with acceptable toxicity profile. Confirmation phase III studies are warranted.*

Key words: chemotherapy, cisplatin, gemcitabine, non small cell lung cancer, phase II study, radiotherapy

Introduction

NSCLC represents 75% of all primary lung tumors. The average annual age-adjusted incidence of lung cancer in western countries is about 75-80 cases per 100,000 men and 20-30 cases per 100,000 women. The prognosis of NSCLC is dismal with a mean 5-year survival rate of only 14%. The major ity of patients are diagnosed in a locally advanced, inoperable and/or metastatic disease, and many patients show recurrent disease after primary surgery and/or RT. The overall 5-year survival rate in this group of patients is less than 5% [1,2].

About 40% of patients with NSCLC present with a locally advanced intrathoracic disease, with stage IIIA and stage IIIB. Although a complete resection in stage IIIA is the treatment of choice, the long-term survival results remain disappointing (5-year survival rate 9%) [3]. The outcome of patients with stage IIIB, where RT is

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a standard therapy, is even poorer (5-year survival 1-3%) [3]. Various treatment modalities have been proposed and tested in order to improve the discouraging results in patients with locally advanced NSCLC. In patients with inoperable stage IIIA or IIIB disease, chest RT plays a major role in the locoregional management [3]. One way of improving cancer control is to modify RT administration: three-dimensional (3D) RT allows increase in the total dose given to tumor tissue, while reducing normal tissue injury. Similarly, hyperfractionation of RT enables administration of a greater tumor dose without increasing late toxicity. Another way is the administration of sequential or concomitant chemotherapy with RT. The addition of chemotherapy to RT may increase cure rate not only by improving intrathoracic tumor control, but also by eliminating or postponing the emergence of metastatic disease [4]. Currently the most frequently tested strategies have been first-line chemotherapy followed by RT or concurrent application of both methods (chemoradiation). The goal of the sequential approach is to reduce micrometastatic disease, but this therapeutic strategy may also reduce the volume of the primary tumor making subsequent irradiation more effective, or even rendering the tumor operable. The advantage of the sequential therapy is the delivery of full-dose chemotherapy. On the other hand, prolonged period of treatment, postponed irradiation, and a possibility of accelerated repopulation of tumor cells are considered as major disadvantages of this treatment strategy. Chemotherapy administered concomitantly with irradiation avoids those drawbacks, and it might improve locoregional control by making tumor cells more vulnerable to RT (radiosensitization). However, this strategy causes greater toxic effects, which decrease the quality of life and increase the costs of supportive care. Also, the chemotherapy dosage has to be usually reduced in patients undergoing concomitant chemoradiation.

The goal of this randomized phase II study was to evaluate the value of sequential chemoradiation. The combination of gemcitabine and cisplatin was selected in 1999 as an emerging standard of care in NSCLC [5-12]. The promising results from early phase II studies in advanced disease were confirmd in later randomized phase III trials, and underlined the consistency of efficacy of gemcitabine/platinum combination [13-24].

Patients and methods

Eligibility criteria

Chemonaïve patients with histologic or cytologic diagnosis of stage IIIA or IIIB NSCLC who were not eligible for curative surgery were enrolled. Patients aged between 18 to 75 years, with bidimensionally measurable lesions (at least 1×1 cm or 2×2 cm by physical examination) were eligible for enrollment. No prior RT was permitted. Other form of therapy was allowed only up to 3 weeks before entering the study. Patients were also required to have an estimated life expectancy of at least 12 weeks, ECOG performance status of 0-2, and adequate bone marrow reserve (white blood cell [WBC] count $\geq 3.5\times10^9$/L, hemoglobin $\geq$ 10.0 g/dL, and platelets $\geq 100\times10^9$/L). Patients with active infection, pregnancy, second primary malignancy, or serious concomitant systemic disorders incompatible with the study were not eligible to participate in the study. Also, patients with inadequate liver function (bilirubin >1.5 times upper limit of normal [ULN], alanine transaminase or aspartate transaminase >3 times ULN), or inadequate renal function (creatinine >1.25 times ULN) were not eligible.

All patients provided written informed consent before entering the trial. Additionally, the study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki or the applicable guidelines of good clinical practice and was approved by the Ethical Review Board.

Treatment plan

Patients were randomized into 2 arms: chemoradiation (arm A) and radiation only (arm B). Patients in arm A received gemcitabine 1250 mg/m^2 intravenously (i.v.) over 30 min on days 1 and 8, plus cisplatin 80 mg/m^2 i.v. over 60 min on day 1. Patients had been prehydrated with 2,000 ml normal saline over 6 h. Subsequently, cisplatin was administered i.v. over 120 min in a volume of 1,000 ml normal saline, together with 37.5 mg mannitol. All patients received posthydration with 2,000 ml normal saline and dextrose 5% solution. The cycle was repeated on day 21. Patients were to receive a total of 3 cycles of chemotherapy but were discontinued earlier in the event of intolerable toxicity or progressive disease. Patients in arm A started radiotherapy 7-14 days after the completion of the third cycle of chemotherapy. For patients in arm B, RT was initiated immediately after randomization.

RT was given in both arms with photon beams from either cobalt-60 or linear accelerator. The original volume was based on conventional chest x-rays and computed tomography (CT) scans, which were taken either after 3 cycles of chemotherapy in arm A or before randomization in arm B, and included the primary lesion, the ipsilateral hilum and the mediastinum with a margin of 2 cm, and any grossly involved nodal sites

(ie, biopsy-positive CT/magnetic resonance imaging (MRI) scan nodes >1.5 cm, or node of any size with a necrotic center). If the primary tumor was in the lung periphery, only one radiation field was used to cover it and the mediastinum. The contralateral hilum was not treated. The spinal cord was ≥ 1 cm outside of the field edge if it was included in the original volume fields. The target dose to the original volume was 63 Gy in 34 fractions of 1.85 Gy/fraction (1 fraction/day, 5 fractions/week).

Patients received full supportive care, including growth factors for prolonged myelosuppression. If prolonged neutropenia or neutropenic sepsis occurred in a previous cycle, and/or absolute granulocyte count (AGC) fell below 500/mm^3, granulocyte colony-stimulating factor (G-CSF) was used in subsequent cycles, and continued daily until AGC recovered to ≥ 10,000/mm^3. When G-CSF was used, complete blood counts were done twice a week. Antiemetic treatment was used. Flu-like symptoms of gemcitabine were managed by administering paracetamol.

Treatment modifications

No new chemotherapy cycle started in arm A unless the WBC count was ≥ 3.0×10^9/L, and the platelet count ≥ 100×10^9/L. Dose adjustments within a cycle were made based on weekly WBC and platelet counts. The day-8 gemcitabine dose was given at 75% if the WBC count was 2.0 to 2.9×10^9/L or the platelet count was 50 to 99×10^9/L. The day-8 gemcitabine dose was omitted if the WBC count was < 2.0×10^9/L or the platelet count was < 50×10^9/L. The cisplatin dose was reduced by 50% for grade 2 neurotoxicity (to remain reduced in subsequent cycles) and serum creatinine 1.25 to 1.5 times the ULN. For grade 3 neurotoxicity, the cisplatin dose was omitted and gemcitabine was reduced by 50% or omitted (to remain reduced in subsequent cycles). Chemotherapy was to be discontinued with any grade 4 nonhematologic toxicity including neurotoxicity. Serum creatinine >1.5 times the ULN required the cisplatin dose to be held. In case of tinnitus or significant clinical hearing loss, the cisplatin dose was to be reduced or stopped. For grade 3 nonhematologic toxicities (except nausea, vomiting, and alopecia), the cisplatin and gemcitabine doses were reduced by 50% or omitted. Patients with sustained WHO grade 4 neutropenia, febrile neutropenia, thrombocytopenic bleeding or omission of the day-8 dose of gemcitabine because of bone marrow toxicity were to receive 1 dose level below the previous one: gemcitabine 1000 mg/m^2, cisplatin 80 mg/m^2 (level 1) or gemcitabine 1000 mg/m^2, cisplatin 50 mg/m^2 (level 2). Patients who could not tolerate gemcitabine 1000 mg/m^2, cisplatin 50 mg/m^2 were to be discontinued. A patient who could not be given drug for 6 weeks from the time of the last study drug administration was withdrawn from the study.

RT started if the WBC count was ≥ 3.0×10^9/L, the platelet count was ≥ 100×10^9/L, and if the patient recovered from any grade 3/4 nonhematologic toxicities after chemotherapy (arm A). RT had to start within 7-14 days after chemotherapy in arm A. Patients were discontinued if they did not recover from any toxicity to baseline values within 6 weeks. RT was interrupted only for grade 4 toxicity and resumed when that toxicity decreased to grade 2 or less.

Baseline and treatment assessments

Patient examinations included tumor measurement by radiological imaging tests (chest x-ray, CT scan, MRI, or ultrasound), medical history and physical examination, evaluation of ECOG performance status, tumor measurement of palpable or visible lesions, full blood count, serum biochemistry, electrocardiogram (ECG), and vital signs. The evaluation technique of tumor measurements for a given patient was consistent throughout the study.

All patients who received at least 1 dose of gemcitabine or the first dose of RT were evaluated for safety. Examinations included changes from baseline in performance status and weight, summaries of the number of blood transfusions, adverse events and laboratory changes, and the assessment of all toxicities using the WHO scale.

All randomized patients were evaluated for efficacy on an intent-to-treat basis. Response was assessed after 3 cycles of chemotherapy (arm A) and after completion of RT in both arms, using standard WHO criteria. Overall response duration was measured from the day of the first cycle of chemotherapy (arm A) or the first dose of RT (arm B) to the date of the first observation of progressive disease. Survival time was calculated as the interval between the date of the first cycle of chemotherapy (arm A) or the first dose of RT (arm B) and death. TTPD was measured from the date of randomization until the time of documented progressive disease.

Statistical analysis

The primary endpoint for comparison in this randomized phase II study was the ORR in the sequential chemoradiotherapy arm *versus* the RT-alone arm, using chi-square test. Secondary endpoints included toxic-

ity, duration of response, TTDP and overall survival (time-to-event analysis using log-rank test).

The goal of this study was to demonstrate an increased ORR of at least 35% for a total rate of 60% in the chemoradiation arm *versus* RT only (historical ORR 25%). This sample size of 30 patients per treatment arm ensured an 80% power to detect the increase of ORR. All tests were two-sided and used a significance level of 5%. Additionally, this number of patients was expected to provide enough data for comparison with the ORR of earlier studies [25-27]. This study was not designed with sufficient power to detect differences in TTPD and overall survival.

Results

Patient characteristics

From June 1998 to December 2000, a total of 60 patients from two centers were enrolled in this trial. Thirty patients were randomized to the chemoradiation arm, and 30 to the RT-only arm. Both arms were well balanced in terms of patient demographics (Table 1). The median patient age in both arms was about 60 years, and the majority had ECOG performance status of 0-1. More than half of the patients in each arm had stage IIIA disease with predominant histology of squamous cell carcinoma or adenocarcinoma.

Table 1. Patient demographics and characteristics

	Chemoradiation arm n (%)	*Radiation-only arm n (%)*
No. of patients	30	30
Age (years)		
Median	58	62
Range	39-75	42-73
Sex		
Men	27 (90.0)	28 (93.3)
Women	3 (10.0)	2 (6.6)
ECOG performance status		
0	15 (50.0)	11 (36.6)
1	11 (36.6)	12 (40.0)
2	4 (13.3)	7 (23.3)
Stage		
IIIA	16 (53.3)	17 (56.6)
IIIB	14 (46.6)	13 (43.3)
Histology		
Squamous cell	17 (56.6)	19 (63.3)
Adenocarcinoma	7 (23.3)	7 (23.3)
Large cell	6 (20.0)	4 (13.3)

Table 2. Tumor response

Response	*Chemoradiation arm (n = 30)* n (%)	*Radiation-only arm (n = 30)* n (%)
Complete response	1 (3.3)	0 (0.0)
Partial response	13 (43.3)	8 (26.6)
Stable disease	10 (33.0)	17 (56.6)
Progressive disease	6 (20.0)	5 (16.6)
Overall response*	14 (46.6)	8 (26.6)
95% CI	29.0–53.0	19.0–33.0

*p=0.324

Response

All enrolled patients were included in the efficacy analysis. In the chemoradiation arm, 1 (3.3%) patient had a complete response (CR), and 13 (43.3%) had partial response (PR), for an ORR of 46.6% (95% CI: 29.0-53.0). Additionally, 10 (33.0%) patients had stable disease, and 6 (20.0%) patients progressed. In the RT-only arm, there were 8 (26.6%) PRs giving an ORR of 26.6% (95% CI: 19.0-33.0). There were 17 (56.6%) patients with stable disease and 5 (16.6%) with progressive disease. The difference in the response rates for the chemoradiation and RT-only arms was not statistically significant (p=0.324) (Table 2).

The ORR was significantly better for arm A patients with good ECOG performance status (PS 1; p=0.016). No statistical significance in ORR was detected between the 2 arms in relation to age (≤ 60 *versus* > 60 years), disease stage (stage IIIA *versus* IIIB), gender (men *versus* women) or the histological type (squamous *versus* adenocarcinoma) (Table 3).

The median duration of response of 9.90 months in the chemoradiation arm (95% CI: 9.02-10.78) was significantly longer than 8.60 months (95% CI: 5.97-11.23) obtained in the RT-only arm (p=0.046; Figure 1).

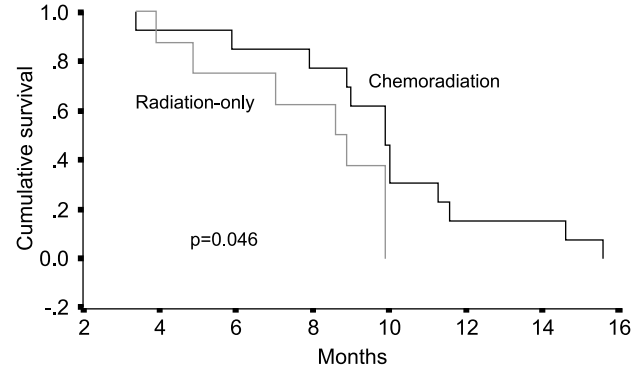

Figure 1. Response duration.

Table 3. Overall response rate in relation to prognostic factors

Prognostic factor	*Overall Response Rate*		*p-value*
	Chemoradiation arm n (%)	*Radiation-only arm n (%)*	
Age (years)			
< 60	10 (33.0)	3 (10.0)	0.200
> 60	4 (13.3)	5 (16.6)	0.908
Sex			
Men	13 (43.3)	6 (20.0)	0.223
Women	1 (3.3)	2 (6.6)	0.138
ECOG PS			
0	7 (23.3)	6 (20.0)	0.624
1	7 (23.3)	1 (3.3)	0.016
2	0 (0)	1 (3.3)	0.632
Stage			
IIIA	8 (26.6)	3 (10.0)	0.793
IIIB	6 (20.0)	5 (16.6)	0.112
Histology			
Squamous cell	10 (33.0)	4 (13.3)	0.210
Adenocarcinoma	2 (6.6)	2 (6.6)	0.788
Large cell	2 (6.6)	2 (6.6)	0.287

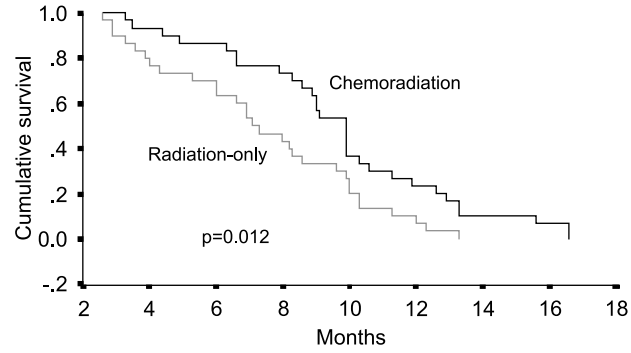

Figure 2. Time to disease progression.

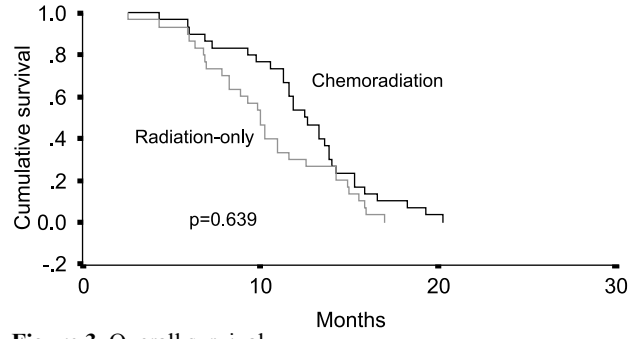

Figure 3. Overall survival.

Time-to-event results

The median TTPD for the chemoradiation arm was 9.90 months (95% CI: 9.12-10.68), while that for the RT-only arm it was 7.10 months (95% CI: 5.60 -8.60). For the chemoradiation arm, TTPD was significantly longer (p=0.012; Figure 2).

The median overall survival for the chemoradiation arm was 12.50 months (95% CI: 10.98-14.02), and that for the RT-only arm it was 10 months (95% CI: 8.93-11.07), both being without statistical significance (p=0.639). One-year survival rate was 43% for arm A *versus* 24% for arm B (p=0.067; Table 4; Figure 3).

Toxicity

All 60 patients were eligible for safety analysis. Hematologic toxicity was more pronounced in the sequential chemoradiation arm A, and grade 3/4 toxicities encountered are listed in Table 5. The major toxicities were anemia, neutropenia, and thrombocytopenia, the incidence of which was significantly higher than in the RT-only arm. However, these hematologic toxicities did not have any significant clinical consequences in terms of bleeding, febrile neutropenia, or infection, as compared to the RT-only arm.

The nonhematologic toxicity was mild, and the list of grade 3 or 4 toxicities observed is given in Table 5. The type and incidence of these toxicities in both arms were similar, except that arm A patients had a higher incidence of paresthesia, alopecia, and significantly more frequent nausea/vomiting (p=0.002). No treatment-related deaths occurred.

Table 4. Survival, time to progressive disease (TTPD), and response duration

Endpoint	*Chemoradiation arm (n=30)*	*Radiation-only arm (n=30)*	*Log-rank (p)*
Survival			
Median (months)	12.50 (95% CI 10.98-14.02)	10.00 (95% CI 8.93-11.07)	0.639
1-year (%)	43	24	0.067
TTPD			
Median (months)	9.90 (95% CI 9.12-10.68)	7.10 (95% CI 5.60-8.60)	0.012
WHO response duration			
Median (months)	9.90 (95% CI 9.02-10.78)	8.60 (95% CI 5.97-11.23)	0.046

Table 5. WHO grade (G) 3/4 toxicity (% of patients)

	Chemoradiation arm (n=30)		*Radiation-only arm (n=30)*		*p-value**
Toxicity	*G3*	*G4*	*G3*	*G4*	
		Hematologic			
Anemia	23.3	3.3	10.0	3.3	0.317
Neutropenia	20.0	6.6	6.6	0	0.038
Thrombocytopenia	23.3	13.3	3.3	0	0.001
Febrile neutropenia	0	3.3	0	0	0.313
		Non-hematologic			
Transaminases	6.6	3.3	3.3	0	0.301
Mucositis	3.3	3.3	13.3	0	0.389
Nausea	26.6	23.3	13.3	0	0.002
Vomiting	13.3	10.0	3.3	0	0.002
Diarrhea	3.3	3.3	3.3	0	0.554
Dyspnea	6.6	3.3	10	0	0.999
Pain	6.6	3.3	3.3	0	0.379
Paresthesia	13.3	0	0	0	0.038
Hearing alterations	6.6	0	0	0	0.150
Alopecia	13.3	0	0	0	0.038
Fatigue	13.3	0	10	0	0.688
Infection	3.3	0	6.6	0	0.554

* The chi-square test was used for comparison between treatment groups. No p-value is derived when the expected counts are too small

Drug delivery

All 30 arm A patients completed the 3 cycles of chemotherapy. The dose intensity was 90.6% (377.5 mg/m^2/week) for gemcitabine, and 92.2% (24.57 mg/m^2/week) for cisplatin. Eight (26.66%) patients had at least one dose delay for gemcitabine on day 8. Gemcitabine dose adjustments were necessary for 6 (20%) patients on day 1, and for 10 (33%) patients on day 8. There were no dose delays for cisplatin, and dose adjustments were necessary for 8 (26.6%) patients.

Discussion

The results of our randomized phase II study indicate that multimodality treatment with sequential chemoradiation is well tolerated, and probably improves the outcome of patients with inoperable stage IIIA or IIIB NSCLC, as compared to RT alone.

The ORR for all patients was not significantly better in either arm; however, patients with ECOG performance status of 0-1 tend to respond better to sequential chemoradiotherapy (14 patients; 46.6%), than to RT alone (7 patients; 23.3%). The ORR did not show any other significant variation based on age, sex, disease stage, or histology. Duration of response and TTPD were significantly better in the chemoradiation arm ($p < 0.05$). The differences in overall survival and 1-year survival rates were nonsignificant; however, there was a trend towards longer survival in patients with sequential chemoradiation (Table 4). Both regimens were well tolerated, but grade 3/4 hematologic and nonhematologic toxicities were significantly higher in the chemoradiation arm, especially neutropenia, thrombocytopenia, nausea/vomiting, paresthesia and alopecia. The low incidence of febrile neutropenia (only 1 case), and no cases with bleeding indicate that neutropenia and thrombocytopenia did not cause a clinical problem. The prevalence of nausea/vomiting and paresthesia are to be expected with cisplatin administration.

The results of our trial correspond well with published phase III randomized studies, comparing sequential chemoradiation with radiation alone [25-35]. In most cases, chemotherapy was given before RT. The majority of these studies were performed with older generation drugs and were carried out in the 1980s and 1990s [28-30,36,37]. Three of those large phase III randomized studies (two performed in the USA and one in France [25, 31-35] gave consistently positive results in favor of chemoradiation. A study performed by the Cancer and Leukemia Group B (CALGB) included 155 patients with favorable pretreatment characteristics (WHO performance status 0-1, weight loss less than 5%) [25,31]. Patients were randomly assigned to RT alone (60 Gy over 6 weeks) or the same course of RT preceded by 2 cycles of cisplatin and vinblastine. As in our study, hematologic toxicity (neutropenia and thrombocytopenia) and nausea/vomiting were more frequent in patients who received upfront chemotherapy, but this did not affect the administration of RT. In the CALGB study, the survival benefit for patients treated with chemoradiation was 23% at 3 years compared to 11% for those receiving radiation alone. These results were confirmed later in an update, which included a 7-year follow-up [31].

The interpretation of those early trials mentioned above, with combined modalities in locally advanced NSCLC, was difficult because many of the trials were criticized for small patient samples and methodological flaws. Nevertheless, they indicated that chemotherapy applied as an adjunct to RT improves survival and alters the course of this disease.

In some studies, primary chemotherapy seemed to reduce the rate of distant metastases, whereas RT alone or concomitant chemoradiation improved local tumor control [35,38-41]. It seems that concurrent chemoradiation might be more effective than sequential chemoradiation (Table 6); however, initial studies reported higher toxicities. A couple of recently

Table 6. General outcomes of multimodality therapy in stage III NSCLC*

Therapy	*Reference*	*Median survival (months)*	*Overall survival 1-Year (%)*	*Overall survival 2-Year (%)*	*G 3/4 toxicity (%) (RT)*
RT	1	10	40	15	10
CT→RT	25	14	55	30	25
CT/RT	34	17	65	35	50
CT→CT/RT	53	15	60	40	35
CT/RT→CT	54	26	78	54	<20

NSCLC=non-small cell lung cancer; RT=radiotherapy; CT=chemotherapy; G=grade
*Combined average all drugs
Taken from: Pisters K. ASCO discussant, Lung Cancer Session. ASCO 2000, New Orleans

published randomized phase III studies addressed the question of concurrent *versus* sequential chemoradiation. Two Japanese trials evaluating the mitomycin, vinblastine, and cisplatin regimen, and two trials (US Intergroup and RTOG 9410) using the cisplatin and vinblastine regimen, showed an advantage for the concomitant approach [41-43]. Those results were confirmed by recently published phase II/III randomized studies from the Czech Republic (cisplatin and vinorelbine) and Germany (paclitaxel and carboplatin) [44,45]. The superiority of concurrent over sequential chemoradiation was also confirmed by long-term survival analysis of the RTOG 9410 trial, which was presented at ASCO 2003 [46].

It should be noted that patients benefiting from concomitant chemoradiation in those trials were preselected patients with favorable prognostic factors, and underwent careful staging procedures. Therefore, this aggressive treatment approach may not be appropriate for all patients. It seems that the concomitant approach provides better locoregional tumor control and overall survival; however, the improved efficacy has to be balanced against increased early and late toxic effects, which are less prominent in sequential chemoradiation (Table 5). The selection of the proper treatment for a patient with primary unresectable locally advanced NSCLC requires careful consideration of all aspects by the treating physician.

The need for improvement of current methods calls for a continuous search for more effective strategies and better evaluation of real clinical benefit for a patient. Further clinical trials should focus on identification of optimal interactions between chemotherapy and RT. This search should also define the most effective types and doses of anticancer agents as well as the optimal features of RT used in combined modalities (CHART or conformal 3-dimensional irradiation). Only a limited number of clinical trials evaluating the role of new agents such as gemcitabine [47-49], taxanes [49-51], topoisomerase inhibitors and vinorelbine [49,52] in the chemoradiation setting is currently available, and trials comparing new compounds with older regimens in the same setting are warranted. Identification of prognostic and biological predictive markers should help differentiate patients requiring different therapeutic approaches. The increased toxicity of those treatment modalities, as compared to radiation alone, the quality of life and its proper evaluation (e.g. EORTC QLQ-C30) have to be taken into account.

In summary, our results indicate that for the treatment of patients with locally advanced NSCLC, sequential chemoradiation with gemcitabine plus cisplatin is more effective than RT alone. The sequential multimodality treatment appears to have higher incidence of hematologic toxicity (neutropenia or thrombocytopenia) without, however, compromising subsequent RT delivery and does not have any serious clinical consequences (bleeding, febrile neutropenia, or infection) as compared to RT alone.

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