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A randomized phase II study comparing induction or consolidation chemotherapy with cisplatin–docetaxel, plus radical concurrent chemoradiotherapy with cisplatin–docetaxel, in patients with unresectable locally advanced non-small-cell lung cancer

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Background: In stage III non-small-cell lung cancer (NSCLC), the role of systemic chemotherapy preceding or following concurrent chemo-radiotherapy (CT-RT) is unclear. We carried out a randomized phase II study to study the toxicity involved-field CT-RT with either induction or consolidation cisplatin–docetaxel (Taxotere).

Patients and methods: Patients were randomly assigned to receive two cycles of docetaxel (D) 75 mg/m^2 on day 1 and cisplatin (C) 40 mg/m^2 on days 1 and 2, either preceding (IND arm) or following (CON arm) concurrent CT-RT, where 66 Gy was delivered using involved-fields concurrent with weekly D 20 mg/m^2 and C 20 mg/m^2. Patients at higher risk for lung toxicity (V_{20} > 35%) crossed over to IND arm. Seventy patients were needed to exclude grade (G)3–4 esophagitis in >25%.

Results: Of the 70 eligible patients, 26 were treated in IND and 34 CON; five with V_{20} >35% switched from CON to IND. The differences in G3–4 esophagitis observed (32/2% IND versus 21/3% CON) were not significantly different from the hypothesized 25% rate. Rates of G≥2 pneumonitis were similar, but IND arm had less G3–4 neutropenia. One-year survival was 63.2% [95% confidence interval (CI) 48.4% to 78.0%] and 65.5% (95% CI 48.2% to 82.8%) for the IND and CON arms, respectively.

Conclusion: Both study arms merit further testing in patients with limited volume stage III NSCLC.

Key words: chemo-radiotherapy, concurrent, involved-field radiotherapy, sequencing, stage III lung cancer, toxicity

introduction

The recommended treatment of patients presenting with inoperable stage III non-small-cell lung cancer (NSCLC) and a good performance score is concurrent chemo-radiotherapy (CT-RT) [1]. Stage III NSCLC constitutes a heterogeneous group, and in patients with inoperable disease, median survival reported in recent phase III trials ranges from 12 to 23.3 months [2, 3]. In potentially operable disease, grade ≥3 radiation pneumonitis was observed in 16% of patients receiving only definitive CT-RT [4]. A phase II study evaluating induction and concurrent CT-RT cisplatin with paclitaxel, gemcitabine, or and vinorelbine reported G3≥ esophagitis rates ranging from 25% to 52% [5]. Concerns about both toxicity and the limited gains in survival led to a slow adoption of concurrent CT-RT in some countries [6]. The incidence of esophagitis is reduced when elective mediastinal nodal irradiation is omitted and smaller 'involved-fields' are treated [7]. The recommended systemic treatment in stage III NSCLC consists of 2–4 cycles of chemotherapy [8]. Different schemes for both induction and consolidation therapy are in clinical use, with induction chemotherapy before the start concurrent CT-RT preferred by some [9] and consolidation chemotherapy preferred by others [10].

Docetaxel enhances the cytotoxic effects of radiotherapy *in vitro* [11, 12], with radiation enhancement being superior to that observed with paclitaxel [13]. Radiotherapy with

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concurrent docetaxel is feasible after induction ciplatin–docetaxel [14], and selection of patients in whom the lung volume receiving 20 Gy was below 30% allows weekly docetaxel and radiotherapy (66 Gy) to be combined safely [15]. As objective response rates were only 47%, other agents have been added during concurrent CT-RT. We designed a randomized phase II study to examine the safety and toxicity profile of two sequences cisplatin–docetaxel, either as induction (IND) before or consolidation (CON) after concurrent CT-RT with radiosensitizing doses of the same doublet in order to identify the most feasible regimen for further study. We postulated that using only involved-field radiotherapy could allow for reduced toxicity and delivery of a higher dose intensity of chemotherapy, which in turn would to encourage further study of this approach.

patients and methods

This multicenter, open label randomized phase II trial (PulmonArt) was conducted in 15 centers from 7 European countries. Enrollment commenced in March 2004 and closed in November 2005. Eligible patients were male or nonpregnant and non-breast-feeding females, 18–75 years of age, with histologically or cytologically confirmed stage IIIA NSCLC with multiple clinical-level N2 or stage IIIB that was not pretreated, with World Health Organization performance status of zero to one, lung function tests (FEV_1 and DL_{CO}) ≥50% of normal, weight loss of ≤10% within the last 3 months, and no concomitant serious illnesses or medical conditions. Mediastinal lymph node metastases were preferably confirmed using histology or cytology. Staging 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET) scans were not mandatory. Patients were referred to a radiation oncologist before study accrual, and those with an estimated V_{20} in excess of 35% were excluded. The definitive V_{20} value, which was derived from the radiotherapy planning computed tomography (CT) scan, was defined by total lung volume minus the planning target volume [16]. Patients with T4 disease secondary to extensive involvement of major blood vessels were ineligible.

Screening assessments were carried out within 28 days of first dose of chemotherapy. The protocol was submitted to the local independent ethics committees and approved before the study was activated in the respective centers. Before local study activation, centers had to submit a quality assessment questionnaire and complete a dummy run procedure [17].

treatment plan

In the induction (IND) arm, patients received two 3-week cycles of cisplatin 40 mg/m^2 on days 1 and 2 and docetaxel (Taxotere®; sanofi-aventis, France) 75 mg/m^2 on day 1 of every cycle as induction chemotherapy, followed by 6 weeks of once-weekly docetaxel 20 mg/m^2 and cisplatin 20 mg/m^2 (on day 1 of every week), concurrent with radiotherapy at a dose of 2 Gy/day for 5 days/week for 6.5 consecutive weeks to a total dose of 66 Gy. Patients in concurrent (CON) arm received the same weekly cisplatin–docetaxel scheme concurrent with radiotherapy to a total dose of 66 Gy, followed by two 3-week cycles of cisplatin 40 mg/m^2 on days 1 and 2 and docetaxel 75 mg/m^2 on day 1 of every cycle as consolidation chemotherapy.

chemotherapy

Induction or consolidation docetaxel was administered in a 60-min i.v. infusion, and administration concurrent with radiotherapy was administered as a 30-min i.v. infusion. Induction or consolidation cisplatin was to be administered over 30–60 minutes on days 1 and 2, with administration on day 1 immediately following the docetaxel infusion. Hydration and prophylactic antiemetics were administered before chemotherapy and according to institutional practice. Standard rules for dose modifications allowed due to toxicity were docetaxel 75 mg/m^2 and cisplatin 40 mg/m^2 × 2 for an absolute neutrophil count nadir of $<0.5 \times 10^9$/l for >7 days, platelet blood cell blood cell count nadir $<25 \times 10^9$/l, febrile neutropenia, or grades 3–4 skin toxicity or stomatitis; docetaxel 75 mg/m^2 and cisplatin 30 mg/m^2 × 2 for grade 2 neurotoxicity, grades 3–4 nonhematological toxicity (except anemia), or >1 toxicity/conflicting recommendations; and docetaxel 85 mg/m^2 and cisplatin 30 mg/m^2 × 2 for nephrotoxicity grade ≤2 during the previous cycle [14]. Cisplatin concurrent with radiotherapy was administered i.v. over 30–60 minutes, immediately after docetaxel infusion, and single dose dexamethasone 4 mg was administered i.v. 15 min before each docetaxel infusion (e.g in each cycle of treatment). Thoracic radiotherapy was started 2–4 h after the end of cisplatin infusion. If a planning CT scan after randomization revealed a V_{20} >35%, patients randomly allocated to arm CON were instead treated according to arm IND.

radiotherapy

Involved-field radiotherapy was administered in accordance with European Organization for Research and Treatment of Cancer (EORTC) recommendations [16]. Three-dimensional treatment planning was mandatory with a planning CT scan carried out in supine position using an immobilization device. The clinical tumor volume (CTV) was the pre-chemotherapy tumor volume, even in IND arm. In case a post-randomization, V_{20} was >35%, patients were only eligible for IND treatment, and the post-chemotherapy volume was used as CTV in order to keep the V_{20} <35%. Lymph nodes measuring ≥1 cm in short-axis diameter were included in the CTV. The planning treatment volume (PTV) encompassed the CTV with a margin of radiologically normal and uninvolved tissue of 1.5 cm.

Doses to normal tissues were limited by customized blocking, with every effort made to keep the V_{20} ≤35%; spinal cord dose was ≤46 Gy. Dose volume histograms for the PTV, spinal cord, and V_{20} were generated for all patients. The PTV was irradiated in a single phase using multiple fields with megavoltage photons of ≥6 MeV. The PTV dose of 66 Gy in 33 once-daily fractions of 2 Gy was specified at the International Commission on Radiation Units (ICRU) reference point and corrected for lung heterogeneity. The minimum and maximum PTV doses were, respectively, >95% and <107% of the prescribed dose at the ICRU reference point. No adjustments for increased treatment time were made for treatment interruptions.

tumor and toxicity assessments

Tumor assessments were carried out at screening and every 6 weeks during treatment using RECIST criteria [18]. Toxicity was evaluated using National Cancer Institute—Common Toxicity Criteria classification v3.0 [19]. Radiological examinations were repeated every 3 months during the first 3 years post-treatment until the date of disease progression, death, or loss to follow-up. During treatment, adverse events and blood counts were checked weekly and blood chemistry analyses every 3 weeks.

statistics

The primary study end point was the incidence of grade ≥3 esophagitis in the two treatment sequences. A phase II study evaluating concurrent CT-RT using elective nodal irradiation and combined with vinorelbine, paclitaxel (Taxol), or gemcitabine reported G3≥ esophagitis rates ranging from 25% to 52%, respectively [5]. We estimated that the maximal rate of grades 3–4 esophagitis considered acceptable by clinicians in the setting of stage III NSCLC was 25%. The null hypothesis was that the toxicity level is too high (≥25%) to be tolerable. The two arms were tested separately and compared with this threshold with a one-sided chi-squared test. Allowing for a type I

error rate of 0.20 with at least 30 eligible patients per arm (patients who crossed over were not taken into account) would result in an 84% power to reject the null hypothesis if the true toxicity rate is around 13%.

The protocol-specified primary analysis was carried out in the safety population, which was defined as those patients who had received at least one cycle according to the study arm which they were treated in (rather than the arm randomized to, should this differ). The secondary analysis was efficacy, including overall response rates [18] and progression-free survival (PFS), and was carried out on the intention-to-treat population (ITT), which included all patients who were randomly allocated into the study and had at least one post-baseline evaluation; the ITT analysis was carried out according to the treatment group patients were randomized to.

results

A total of 72 patients were randomly allocated from March 2004 to November 2005 in 15 centers in 8 European countries; 36 patients were randomly allocated to IND arm and 36 to CON arm (the ITT population) (Figure 1). Two patients randomly allocated to CON were ineligible as they had stage IV disease. Five patients were switched from CON to IND arms as their planning CT scan, which was carried out post-randomization, revealed a V_{20} >35%. The safety population consisted of a total of 41 patients treated in the IND arm and 29 in CON arm (Table 1), and patients characteristics are summarized in Table 2. A higher proportion of stage IIIB patients were treated in the CON arm (72% versus 44%) (χ^2 = 5.6, *df* = 1, *P* = 0.018), as were fewer females (10% versus 22%) and more patients with squamous cell histology (48% versus 34% in IND arm). Pulmonary function tests (median DL_{co} and FEV_1) were similar in both groups. The majority underwent staging FDG–PET scans (69% versus 76% in IND arm).

study end points

Adverse events that were grade ≥3 were reported for 63% of patients in the IND arm and 72% in CON arm (supplemental Table S3, available at *Annals of Oncology* online). Grade 3 esophagitis occurred in 32% (IND) and 21% (CON), and grade 4 toxicity is seen in 2% and 3%, respectively. The incidence of grade ≥3 esophagitis was not significantly different from the allowable incidence of 25% (chi-square test; *P* = 0.32128 in IND arm and *P* = 0.91462 in CON arm). No late esophageal toxicity was observed. The incidence of esophagitis did not correlate with circumference of esophagus receiving 40 Gy (*P* = 0.4798), 50 Gy (*P* = 0.8899), or the maximum esophageal dose (*P* = 0.2120). As contouring of the entire esophagus was not required in the protocol, analysis of metrics correlating organ volume with toxicity was not possible. Some institutions had a policy of prophylactically placing percutaneous feeding tubes in patients who were considered to be at high-risk esophagitis, and in the presence of symptoms of esophagitis, all such patients were scored as having grade 3 esophagitis.

A total of 18 patients developed grade ≥2 radiation pneumonitis but no significant correlation was observed between V_{20} and incidence of grades 2–5 pneumonitis (*P* = 0.9397) (Figure 2). Of the two cases of grade 5 pneumonitis observed, a patient in the IND arm developed grade 3 pneumonitis after CT-RT (V_{20} = 35%) and died 5 months post-treatment. The second was a patient in the CON arm who

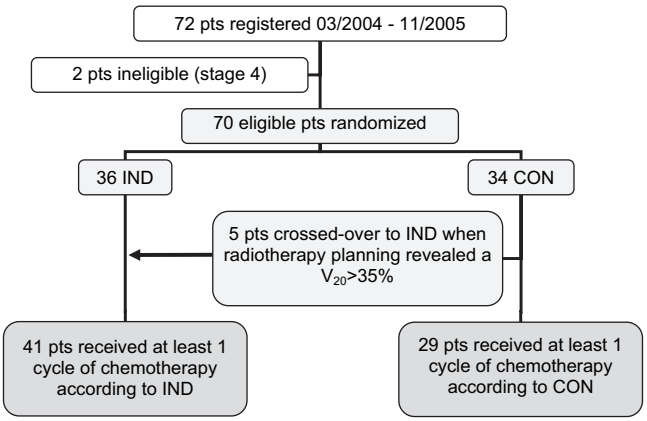

Figure 1. CONSORT diagram.

Table 1. Datasets analyzed; all patients treated (*N* = 70)

Population	Analysis according to	Arm IND (*n*)	Arm CON (*n*)	Total (*N*)
Safety population	Treatment received	41	29	70
ITT population	Treatment allocated	36	34	70

Five patients were switched from Arm CON to Arm IND treatment when their treatment plan revealed a V_{20} >35%.
Arm IND, induction chemotherapy, followed by concurrent radiochemotherapy; Arm CON: concurrent radiochemotherapy, followed by consolidation chemotherapy; ITT, intention-to-treat population.

Table 2. Patient baseline characteristics; safety population (*N* = 70)

Parameter	Statistic	Arm IND	Arm CON
Age (years)	*n*	41	29
	Median	60	63
	Range	39–76	47–74
Squamous cell	*n* (%)	14 (34)	14 (48)
Large cell/adenocarcinoma	*n* (%)	13 (32)	13 (45)
Other	*n* (%)	14 (34)	2 (7)
Stage IIIA	*n* (%)	23 (56)	8 (28)
Stage IIIB	*n* (%)	24 (44)	21 (72)
Sex			
Female	*n* (%)	9 (22)	3 (10)
Male	*n* (%)	32 (78)	26 (90)
WHO PS			
0	*n* (%)	17 (41)	12 (41)
1	*n* (%)	24 (59)	17 (59)
≥2	*n* (%)	0 (0)	0 (0)
DL_{co}	*n*	39	28
	Median	70	88
	Range	28–119	64–132
FEV_1	*n*	40	29
	Median	80.1	83.2
	Range	50–123	55–129

Arm IND, induction chemotherapy, followed by concurrent radiochemotherapy; Arm CON: concurrent radiochemotherapy, followed by consolidation chemotherapy; WHO, World Health Organization; PS, performance status; FEV_1, forced expiratory volume in one second; DL_{CO}, diffusion lung capacity for carbon monoxide.

developed pneumonitis 2 months post-treatment (V_{20} = 35%). A post-mortem examination in the latter revealed residual in-field tumor.

treatment exposure

The median docetaxel dose administered was 259 mg/m^2 in IND arm and 243 mg/m^2 in CON arm, and the comparable dose of cisplatin administered were 266 mg/m^2 and 265 mg/m^2. More patients in CON required dose modifications for docetaxel (55% versus 22%) and cisplatin (28% versus 15%). The median cumulative dose of radiotherapy received in both arms was 66 Gy, with the mean being 61.7 Gy (IND) and 64.5 Gy (CON). The percentage of patients receiving the planned dose of 66 Gy were 57% (IND) and 55% (CON), respectively. Treatment was discontinued prematurely in 18 patients, and these constituted 20% of the IND arm and 35% of the CON arm (supplemental Table S4, available at *Annals of Oncology* online).

analysis of efficacy

With a median follow-up of 14.3 months in IND arm and 15.1 months in CON arm, no difference was observed in overall response rates, overall survival (OS), or PFS between study arms (Figure 3; supplemental Figure S4 available at *Annals of Oncology* online). The 1-year survival rates were 63.2% (95% confidence interval (CI) 48.4% to 78.0%) and 65.5% (95% CI 48.2% to 82.8%) for IND and CON arms, respectively. The median OS of all eligible patients was 28.0 months, and the median PFS was 9.5 months (supplemental Figures S5 and S6 available at *Annals of Oncology* online). In the IND arm, the median OS was 17.5 months, but the OS was not reached in the CON arm for both populations analyzed. Logistic regression analysis revealed the OS to be significantly correlated with disease stage (IIIA versus IIIB) in both safety (P = 0.00248) and ITT populations (P = 0.00382). The PFS was correlated with the disease stage in both safety (P = 0.00011) and ITT populations (P = 0.00382).

discussion

The aim of the present study was to investigate whether the treatment sequence, chemotherapy (cisplatin–docetaxel), followed by concurrent CT-RT or *vice versa*, had an impact on the toxicity profile when exclusively involved-field radiotherapy was used in patients with inoperable stage III NSCLC. The incidence of acute G3–4 esophagitis in both arms was not statistically significant from the hypothesized rate of 25% and similar to that reported recently in another trial where two cycles of consolidation chemotherapy were administered [4]. Reversible G3/4 neutropenia was significantly more common in the CON arm despite the inclusion of only patients with V_{20} values ≤35%. The fact that the OS was not reached in the CON arm is consistent with superior survival reported in patients with a V_{20} of ≤35% [20].

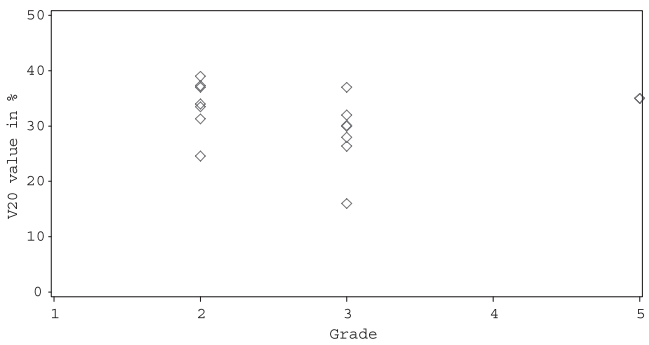

Figure 2. Grade ≥2 radiation pneumonitis versus the V_{20} value. Both cases of fatal pneumonitis had an identical V_{20} value of 35% (single symbols).

The sequencing of systemic CT with CT-RT was also addressed in three recent European studies [21–23], two of which used involved-field radiotherapy and specified V_{20} criteria [21, 22]. Both latter studies revealed statistically similar outcomes irrespective of treatment sequence. A phase II trial randomized 101 patients with a V_{20} <35% to either concurrent docetaxel–carboplatin with radiotherapy to 60 Gy, followed by consolidation docetaxel–gemcitabine for two cycles, or the reverse sequence [22]. Median survival was similar for CON (13.7 months) and IND arms (14.6 months), as was the 4-year survival of 27% and 34%, respectively. Another study randomized 132 patients to either cisplatin–vinorelbine with concurrent radiotherapy to 66 Gy, followed by two cycles of cisplatin–paclitaxel, or the reverse (IND) sequence [21]. Median OSs were 16.9 and 19.3 months for the CON and IND arms and the corresponding 2-year survivals were 43% and 47%, respectively.

However, others studies have raised doubts about the benefits of adding induction and consolidation chemotherapy when concurrent CT-RT is carried out [3, 24]. The phase III Hoosier Oncology Group-LUN 01-24 (HOG-LUN) trial evaluating concurrent CT-RT with cisplatin–etoposide, followed by either consolidation docetaxel or observation, and found no survival benefit for adding docetaxel [3]. Consolidation docetaxel increased hospitalizations and premature death, with grades 2–5 pneumonitis seen in 3.6% in the observation arm and 15% in with docetaxel. However, larger radiation fields were used as elective mediastinal radiotherapy was mandatory, with the contralateral hilus included in the treatment field in 30% of patients [25]. Nearly 80% of observed cases of radiation pneumonitis in HOG-LUN were in patients with V_{20} >35%. Other investigators have linked elective mediastinal irradiation and/or V_{20} values with toxicity of concurrent docetaxel with radiotherapy [15, 26, 27], and we postulate that the differences in toxicity observed in studies may partly reflect reduced 'radiation recall' damage when involved-fields are used to limit the risk of subclinical pulmonary damage. The role of two cycles of induction carboplatin–paclitaxel before concurrent CT-RT with the same agents was evaluated in Cancer and Leukaemia Group B (CALGB) 39801, and induction chemotherapy did not significantly improve median survival [5]. The poor median survival in CALGB 39801 is far lower than that recent trials using cisplatin [3, 4], but three randomized trials evaluating carboplatin as a radiosensitizing agent did not find any improvement in survival over radiotherapy alone [28–30].

It is hazardous to make intertrial comparisons of response rates and median survivals due to differences in choice of chemotherapy, potential differences in patient selection, and

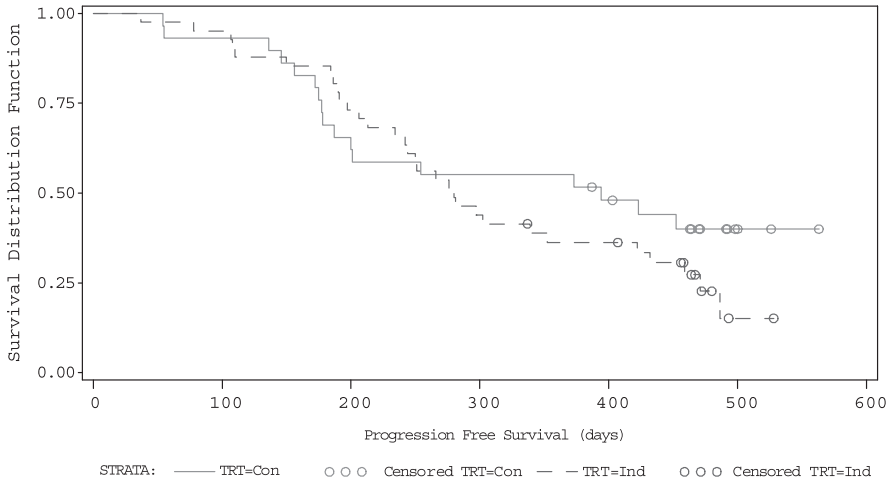

Figure 3. Kaplan–Meier plot for progression-free survival time; safety population ($N = 70$). Interrupted line = arm IND ($n = 41$) and continuous line = arm CON ($n = 29$). TRT, treatment.

use of the V_{20} value in determining treatment sequence in our trial. Our study was activated and completed before the results of EORTC 08941 were available [31], a period in which patients with small-volume stage III N2 disease were routinely referred for surgery and not for CT-RT in some European countries.

In future, less toxic CT-RT regimens are clearly required as 26% of our patients discontinued treatment prematurely and only 55%–57% of patients received the planned radiotherapy dose of 66 Gy. Similar compliance rates were reported in the HOG-LUN study, where after concurrent radiotherapy consisting of just two cycles of cisplatin–etoposide; 25% patients could not be randomized due to toxicity (30.4%) or progression (21.4%) [3]. Histology and molecular characteristics such ERCC1 and BRCA1 expression have been shown to influence outcomes of systemic chemotherapy in NSCLC, and such heterogeneity will need to be accounted for in future trials of CT-RT.

conclusions

Both docetaxel-containing schedules resulted in comparable rates of acute esophagitis when only involved-field radiotherapy was used for small-volume stage III NSCLC with V_{20} values that were largely ≤35%. Although the incidence of grade 3/4 neutropenia has higher in the CON arm, the median survival was not reached in this arm. Both arms merit further testing in phase III trials for patients with small-volume (V_{20} ≤35%) disease in order to establish the role of induction and consolidation chemotherapy in locally advanced NSCLC.

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disclosure

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references

1. Robinson LA, Ruckdeschel JC, Wagner H Jr et al. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132 (3 Suppl): 243S–265S.
2. Vokes EE, Herndon JE 2nd, Kelley MJ et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 2007; 25: 1698–1704.
3. Hanna N, Neubauer M, Yiannoutsos C et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 2008; 26: 5755–5760.
4. Albain KS, Swann RS, Rusch VW et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009; 374: 379–386.
5. Vokes EE, Herndon JE 2nd, Crawford J et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. J Clin Oncol 2002; 20: 4191–4198.
6. Rowell NP, O'rourke NP. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev 2004; 18: CD002140.
7. Yuan S, Sun X, Li M et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for

inoperable stage III nonsmall cell lung cancer. Am J Clin Oncol 2007; 30: 239–244.

8. Pfister DG, Johnson DH, Azzoli CG et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 2004; 22: 330–353.
9. Nyman J, Friesland S, Hallqvist A et al. How to improve loco-regional control in stages IIIa-b NSCLC? Results of a three-armed randomized trial from the Swedish Lung Cancer Study Group. Lung Cancer 2009; 65: 62–67.
10. Green MR, West H, Socinski MA et al. Impact of the ASCO 2007 presentation of HOG LUN 01-24/USO-023 on the prescribing plans of American medical oncologists for patients with stage IIIB non-small cell lung cancer. J Thorac Oncol 2009; 4: 983–987.
11. Mason KA, Kishi K, Hunter N et al. Effect of docetaxel on the therapeutic ratio of fractionated radiotherapy in vivo. Clin Cancer Res 1999; 5: 4191–4198.
12. Mason K, Staab A, Hunter N et al. Enhancement of tumor radioresponse by docetaxel: involvement of immune system. Int J Oncol 2001; 18: 599–606.
13. Pradier O, Rave-Fränk M, Lehmann J et al. Effects of docetaxel in combination with radiation on human head and neck cancer cells (ZMK-1) and cervical squamous cell carcinoma cells (CaSki). Int J Cancer 2001; 91: 840–845.
14. Scagliotti GV, Szczesna A, Ramlau R et al. Docetaxel-based induction therapy prior to radiotherapy with or without docetaxel for non-small-cell lung cancer. Br J Cancer 2006; 94: 1375–1382.
15. Vergnenègre A, Daniel C, Léna H et al. Docetaxel and concurrent radiotherapy after two cycles of induction chemotherapy with cisplatin and vinorelbine in patients with locally advanced non-small-cell lung cancer. A phase II trial conducted by the Groupe Francais de Pneumo-Cancerologie (GFPC). Lung Cancer 2005; 47: 395–404.
16. Senan S, De Ruysscher D, Giraud P et al. Literature-based recommendations for treatment planning and execution in high-dose radiotherapy for lung cancer. Radiother Oncol 2004; 71: 139–146.
17. van Sörnsen de Koste JR, Senan S, Underberg RW et al. Use of CD-ROM-based tool for analyzing contouring variations in involved-field radiotherapy for Stage III NSCLC. Int J Radiat Oncol Biol Phys 2005; 63: 334–339.
18. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205–216.
19. Common Toxicity Criteria classification v3.0 http://ctep.info.nih.gov/reporting/ctc.html (26 July 2010, date last accessed).
20. Kelly K, Chansky K, Gaspar LE et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol 2008; 26: 2450–2456.
21. Fournel P, Vergnenégre A, Robinet G et al. Induction Or Consolidation Chemotherapy With Cisplatin (C) And Paclitaxel (P) Plus Concurrent Chemo-Radiation With Cisplatin And Vinorelbine (V) For Unresectable Non-Small Cell Lung Cancer Patients: Randomized Phase II Trial GFPC-GLOT-IFCT 02-01. J Clin Oncol, 2006 ASCO Annual Meeting Proceedings Part I 2006; 24: 18S (June 20 Suppl), 7048.
22. Garrido Lopez P, Rosell R, Massutí B et al. Predictors of long-term survival in lung cancer patients (p) included in the randomized Spanish Lung Cancer Group 0008 phase II trial using concomitant chemoradiation with docetaxel (D) and carboplatin (Cb) plus induction (I) or consolidation (C) chemotherapy (CT) with docetaxel and gemcitabine (G). J Clin Oncol 2008; 26: (May 20 Suppl; Abstr 7574).
23. Berghmans T, Van Houtte P, Paesmans M et al. A phase III randomised study comparing concomitant radiochemotherapy as induction versus consolidation treatment in patients with locally advanced unresectable non-small cell lung cancer. Lung Cancer 2009; 64: 187–193.
24. Belani CP, Choy H, Bonomi P et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol 2005; 23: 5883–5891.
25. Barriger RB, Aseneau JC, Yu M et al. Rates and risk of pneumonitis in non-small cell lung carcinoma (NSCLC) patients treated with concurrent chemoradiation. Int J Rad Oncol Biol Phys 2008; 72: S117–S118.
26. Onishi H, Kuriyama K, Yamaguchi M et al. Concurrent two-dimensional radiotherapy and weekly docetaxel in the treatment of stage III non-smallcell lung cancer: a good local response but no good survival due to radiation pneumonitis. Lung Cancer 2003; 40: 79–84.
27. Sekine I, Nokihara H, Sumi M et al. Docetaxel consolidation therapy following cisplatin, vinorelbine, and concurrent thoracic radiotherapy in patients with unresectable stage III non-small cell lung cancer. J Thorac Oncol 2006; 1: 810–815.
28. Clamon G, Herndon J, Cooper R et al. Radiosensitization with carboplatin for patients with unresectable stage III non-small-cell lung cancer: a phase III trial of the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group. J Clin Oncol 1999; 17: 4–11.
29. Groen HJ, van der Leest AH, Fokkema E et al. Continuously infused carboplatin used as radiosensitizer in locally unresectable non-small-cell lung cancer: a multicenter phase III study. Ann Oncol 2004; 15: 427–432.
30. Gervais R, Ducolone A, LeChevalier T et al. Conventional radiation (RT) with daily carboplatin (Cb) compared to RT alone after induction chemotherapy (ICT) [vinorelbine (Vr)-cisplatin (P)]: final results of a randomized phase III trial in stage III unresectable non small cell lung (NSCLC) cancer. Study CRG/BMS/NPC/96 of the French Lung Cancer Study Group FNCLCC and IFCT. J Clin Oncol, 2005 ASCO Annual Meeting Proceedings 2005; 23: 16S, Part I of II (June 1 Supplement), 7016.
31. van Meerbeeck JP, Kramer GW, Van Schil PE et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007; 99: 442–450.