

REPORT ASCO 2000 NEW ORLEANS : LUNG CANCER

Johan F. Vansteenkiste, MD, PhD, Univ. Hospital and Leuven Lung Cancer Group

Non-small cell lung cancer - Locally advanced stages

Interesting results of a prospective SWOG trial on the multimodality treatment of **sulcus superior tumors** were presented (1). In many centers, sulcus superior tumors (T3 N0-1) and Pancoast tumors (T4 N0-1) are treated by preoperative low-dose radiotherapy (e.g. 30 Gy) followed by either attempted surgical resection or more radiotherapy. When complete resection is possible, a 5-year survival of about 30% can be expected. This management is based on mere retrospective evidence, going back to the original data of Paulson et al. (2), which were of poor methodology, but nonetheless repeatedly cited in reviews on this topic. The question whether the merits of combined modality treatment, which are now clear in other types of stage III NSCLC, are also applicable in this setting was studied. Mediastinoscopy-negative Pancoast tumors were treated with chemoradiation induction based on cisplatin-etoposide chemotherapy and concurrent radiation up to 45 Gy. All non-progressive cases underwent thoracotomy, followed by 2 more cycles of cisplatin-etoposide. The results were very appealing: 93% of the 101 eligible patients (out of 116 starters) could complete the induction. Eighty-one patients could be operated upon. Resection was complete in 68% of the patients, and a high pathologic complete response rate was noted (57% of the resection specimens). Three-year survival was 50%, both for the T3 and T4 tumors. Although this is a non-controlled phase II study, with potentially important selection bias, it is the only prospective evidence in this setting, certainly worth considering. Furthermore, it is clear that randomized data will be very difficult to obtain in this setting.

A new pathway to improve the results of multimodality approaches in stage III NSCLC could be **consolidation therapy with docetaxel**. Docetaxel actually is the most important non-cross resistant drug in relation to platinum. Therefore, consolidation of cisplatin-based multimodality treatment with docetaxel is appealing. The results of a phase II SWOG study in stage IIIB using this approach were reported (3). In previous SWOG studies, stage IIIB patients were treated with concurrent cisplatin-etoposide and radiotherapy, followed by two additional cycles of cisplatin-etoposide (4). In the new approach, the additional therapy is replaced by 3 cycles of docetaxel consolidation. Compared to the previous SWOG results, docetaxel consolidation gave an improvement in median survival from 15 to 20 months, and in 2-year survival from 34 to 47%. When we put these findings in the perspective of the different approaches for inoperable stage III patients (table 1), it is obvious that randomized studies of this approach are needed.

Table 1 : Expected treatment outcomes with different approaches in inoperable stage III NSCLC.

Therapeutic approach	Expected	Expected	Expected
	MST	2-year survival	grade 3+4 toxicity
RT only (historical series)	10 mo	15%	10%
Seq. CT>RT (5)	14 mo	30%	25%
Conc. CT+RT (5)	17 mo	35%	50%
Conc. CT+RT > CT (4)	15 mo	40%	35%
Conc. CT+RT > DOC* (abstr #1916)	20 mo	47%	25%

* DOC: consolidation with docetaxel

Two further presentations on the combined chemoradio approach in NSCLC deserve mentioning. A RTOG study randomly compared sequential cisplatin-vinblastine followed by 30 fractions of 2 Gy radiotherapy (SEQ), to the same delivered concurrently (CON-QD), or to a concurrent approach with accelerated twice daily radiotherapy (CON-BID) (6). Early results indicate better median survival in the CON (17 months) vs. the SEQ group (14.6 months, P=0.08). Remarkably, the early data indicate better results for the CON-QD than for the CON-BID group.

At the 1999 ASCO meeting, Furuse reported on Japanese data on the superiority of a concurrent approach over a sequential one (5). In a supplementary analysis (7), it was now shown that the survival differences were due to an improved local control in the concurrently treated group. In the concurrently treated group, the survival was superior for patients with a local relapse-free survival, but not for those with a distant relapse-free survival.

Non-small cell lung cancer - Advanced stages

A study to determine the **changes in clinical trials and outcomes** of patients with advanced NSCLC treated in phase III randomized trials in North-America between 1973 and 1994 was reported (8). The size of the trials increased when the first interval (1973-1983) was compared to the second (1984-1994). A sobering conclusion was that only 15% of all trials showed a significant difference in survival for the “new” arm, and that this difference almost never exceeded two months.

A very large ECOG 4-arm chemotherapy trial was in accordance with the above mentioned conclusion (9). This trial used cisplatin-paclitaxel as a standard, and compared this regimen to cisplatin-gemcitabine, cisplatin-docetaxel, and carboplatin-docetaxel. There were no significant differences in survival across arms, with median survival times ranging from 7.4 to 8.2 months, and 1-year survival rates ranging from 31 to 36%. As for differences in efficacy, we point at the longest median time-to-progression in the cisplatin-gemcitabine arm (4.5 months) and the lowest response rate for carboplatin-paclitaxel (only 15.3%, $P=0.08$ vs. standard). As for toxicity, the cisplatin-gemcitabine arm caused more thrombocytopenia (without bleeding however) and renal disturbances, but less neutropenic fever. Carboplatin-paclitaxel caused more severe neurotoxicity. The overall conclusion is that cisplatin plus an other new drug is a good choice, and that the use of adjuvant biological therapies hopefully will be able to improve the prognosis in the future.

Taking into account the limited impact of different treatments of advanced NSCLC on survival, other issues such as cost or palliative value become more relevant.

An interesting **economic analysis** of a formerly reported SWOG trial was performed (10). In that trial, carboplatin-paclitaxel was compared to cisplatin-vinorelbine, and no significant differences in survival or quality-of-life were found. Carboplatin-paclitaxel now proved to be significantly more expensive than cisplatin-vinorelbine (on average >10,000\$ per patient), which was almost entirely due to an increase in cost of chemotherapy products. The potential convenience in the administration of carboplatin-paclitaxel thus seems very hard to pay for.

The issue of the **palliative value of chemotherapy** was examined in a Belgian study comparing cisplatin-based chemotherapy to single agent gemcitabine in patients with symptomatic advanced NSCLC (11). Clinical benefit response, measured by a simple algorithm based on serial patient assessed symptom questionnaires and the evolution of performance status and weight, was the primary end-point in this study. Single agent gemcitabine proved to yield more and longer-lasting clinical benefit, which was probably due to equivalent activity combined with decreased toxicity.

A Greek study compared platinum-based chemotherapy (carboplatin-paclitaxel) to a **non-platin-based combined regimen** (gemcitabine-paclitaxel) in inoperable stage III and stage IV (12). The response and survival data were slightly in favor of the gemcitabine-paclitaxel arm, although the differences were not significant. Quality-of-life or clinical benefit issues were not reported, but the equivalent action of a non-platinum based regimen in advanced stage patients is of interest.

Finally, an Italian study compared **gemcitabine plus vinorelbine** versus vinorelbine alone (13). This study was run in elderly patients, where these 2 schedules can be interesting palliative options. Response rate (22 vs. 15%), median survival time (29 vs. 18 weeks) and quality-of life (stable in 60 vs. 40%) all were in favor of the combined gemcitabine-vinorelbine arm.

Small cell lung cancer

Practical progress in small cell lung cancer can be situated in three domains.

a) Better integration of chemo- and radiotherapy

In limited disease (LD), it has become clear that both thoracic and cranial radiotherapy are of value (14, 15), although questions on the best method and timing remain. Recently, more evidence became available to support early and concurrent use of thoracic irradiation (16). **No important new data** were presented on this issue.

b) Better chemotherapy

In general, the new drugs such as taxanes, camphotecin analogues and gemcitabine have been less extensively studied in SCLC, compared to NSCLC. Cisplatin-etoposide remains the standard regimen in SCLC. Response rates of 70-95% in LD and 60-90% in extensive disease (ED) can be expected, resulting in median survival times of 12-20 months in LD, and 7-12 months in ED. Different options to improve the chemotherapy results were reported.

One option is the **addition of a third (new) drug**, and this was addressed by different authors by adding paclitaxel to the standard: platinum-etoposide+paclitaxel (PE+P) versus platinum-etoposide (PE) (table 2). Abstracts #1889 (17), #1894 (18), and #1918 (19) were randomized studies, abstract #1917 (20) directly compared the PEP-results in LD only with the results out of the Intergroup trial (6), and the results in LD from abstract #1920 (21) can also be compared with the Intergroup results.

Table 2 : Changes in outcome when paclitaxel is added to standard PE in SCLC.

	N	Response rate	Median survival	1-year survival	Toxicity
Abstr #1889	290 PE+P 294 PE	93% 87%	-	-	comparable
Abstr #1894	62 PE+P 71 PE	50% 48%	10.5 mo 11.5 mo	43% 45%	8 toxic deaths 0 toxic deaths
Abstr #1917 <i>Intergroup (6)</i>	55 PE+P	78%	30+ mo <i>23 mo</i>	83% <i>70%</i>	3 toxic deaths
Abstr #1918	84 PE+P 86 PE	89% 82%	10.6 mo 7.8 mo	-	-
Abstr #1920 <i>Intergroup (6)</i>	63 PE+P	64%	not reached <i>23 mo</i>	63% <i>70%</i>	febrile neutrop.

It could be concluded that the promising findings from early phase II studies on the addition of a paclitaxel to standard platinum-etoposide to improve the outcome in SCLC have not been confirmed: a marginal or no increase in survival was accompanied with a clearly increased toxicity.

ECOG examined whether consolidation with **4 cycles of topotecan** gave an extra benefit to ED SCLC patients, who achieved a response or disease stabilization after standard PE chemotherapy (22). Median progression-free survival was 1 month longer, overall survival and quality-of-life were the same, and extra toxicity was noted. These data do not suggest a clinically important non-cross-resistance or role for topotecan in this setting.

Perhaps the most intriguing study came from Japan, where a randomized comparison between **cisplatin-irinotecan** and standard cisplatin-etoposide was made (23). The new arm proved to be better in terms of response (83 vs. 64%), median survival (12.8 vs. 9.4 months) and 2-year survival (18.9 vs. 6.5%). Some peculiar aspects in the data were noted: the standard arm was characterized by >90% important hematological toxicity, which is not expected with cisplatin-etoposide. Does this suggest other susceptibilities in the Japanese population? Moreover, the overall response was better in the new arm, but strange enough, the complete response rate was notoriously higher in the standard arm. It was concluded that the data were intriguing, but that at least one confirmatory trial outside Japan is needed before this regimen can be considered to be a new standard.

c) Use of adjuvant biological strategies

This is probably the most important strategy to improve systemic treatment, given the lack of progression in SCLC chemotherapy in the last decade. Unfortunately, **no major data** were reported. Studies with angiogenesis or matrix metalloproteinase inhibitor, with immunotherapy, and perhaps others, are expected to be reported at next years' ASCO meeting.

Take home messages

1. Multimodality treatment might be able to improve the prognosis of mediastinoscopy-negative Pancoast tumors, just as in other types of stage III NSCLC (abstract #1906).
2. Docetaxel consolidation after cisplatin-based multimodality treatment in stage III NSCLC is appealing (abstract #1916).
3. A very high price is to be paid for patient convenience when carboplatin-paclitaxel is used in advanced NSCLC (abstract #1913).
4. In a very large randomized trial, 4 regimens (cisplatin-paclitaxel, cisplatin-gemcitabine, cisplatin-docetaxel, carboplatin-paclitaxel) proved to have similar activity in advanced NSCLC. Carboplatin-paclitaxel was characterized by the poorest response and increased severe neurotoxicity. Time-to-progression was most favorable for cisplatin-gemcitabine (abstract #2).
5. Taking into account the modest impact on survival, palliative non-cisplatin-based regimens are a good choice in advanced NSCLC (abstracts #1895, #1908, #1909, #1910).
6. Promising findings from early phase II studies on the addition of a third new drug (such as paclitaxel or topotecan) to standard platinum-etoposide to improve the outcome in SCLC have not been confirmed: a marginal or no increase in survival was accompanied with a clearly increased toxicity (abstracts #1886, #1889, #1894, #1917, #1918, #1920).

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