

REPORT ASCO 1998 LOS ANGELES : LUNG CANCER
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Educational session
Treatment of stage III non-small cell lung cancer (NSCLC) in 1998

Thomas J. Lynch (Boston, US), chairman of this session, introduced the problem pointing at the fact that NSCLC can roughly be divided in three large subgroups, each representing about one third of all patients: those with early disease (stages I and II), those with locally advanced disease due to mediastinal lymph node involvement or a primary tumour invading key thoracic structures (stage III), and those with metastatic disease (stage IV). An important proportion of the patients with stage I or II disease can be cured with surgical resection. Except for some rare instances, no cure is possible for stage IV patients. The last decade has been characterised with intensive research to ameliorate the prognosis of stage III patients.

Single modality treatment

It became evident that, beside some exceptions, most of the stage III patients can not be cured with a single modality treatment.

The first exception is the group with a T3 tumour, which was commented upon by **Douglas J. Mathisen** (Boston). If the T3 factor is caused by chest wall invasion, a 5-year survival of 25 to 35% can be expected if there are no mediastinal lymph node metastases. As a matter of fact, this subset of T3N0 patients has moved to the IIB category in the most recent staging system. Superior sulcus tumours are an other category in the T3 group. The importance of precise evaluation of the relationship with adjacent spine, neural foramen and brachial plexus by MRI was stressed. Historical therapy was based on very little evidence, and consisted of preoperative radiotherapy (30 to 40 Gy) followed by surgical resection. There are no randomised data on the question whether straightforward surgical resection with or without postoperative irradiation, radiotherapy followed by surgery, or radical radiotherapy alone is the best choice for these patients. In the historical series a 5-year survival of 25 to 35% could be obtained, much less in case of coexistent lymph node metastases. T3-tumours near to the main carina (less than 2 cm), can be managed with modern bronchoplastic surgical techniques such as sleeve lobectomy or even carinal pneumonectomy. These procedures demand high technical skills both in surgery, anaesthesia and postoperative pulmonary care. In experienced centres, the mortality of these procedures could be reduced below 10%.

The second exception is so-called “unforeseen”, “unexpected”, or “incidental” N2-disease. In these patients, limited (often microscopic) ipsilateral mediastinal lymph node involvement is found at thoracotomy, after a preoperative negative mediastinoscopy. They achieve a 5-year survival of 25 to 30% when treated with surgery alone. A beneficial effect of postoperative radiotherapy has never been shown. Several US and European trials currently examine the potential benefit of adjuvant **cisplatin-based** chemotherapy in this setting.

Only a few categories of stage III NSCLC patients can be cured with a single modality treatment. First, surgery can offer cure in cases with completely resectable T3 tumour. Second, after a negative preoperative mediastinoscopy, unexpected involvement of ipsilateral mediastinal nodes can be found at thoracotomy. Complete resection can be curative in this so-called ‘unforeseen N2’ disease. The role of adjuvant chemotherapy in these categories is currently under investigation.

Combined modality treatment

Evaluation and staging

Interpretation of our current knowledge on the optimal treatment of stage III NSCLC is hampered by the great variability in the extent of staging in the published data. **Thomas J. Lynch** (Boston, US) stressed the importance of the performance status when selecting patients for combined modality treatment. It is a more powerful predictor of outcome than age or co-morbidity. Furthermore, adequate distant and locoregional staging is of key importance (proposed schedule in table 1). Cranial CT scan should be used more often, given the increasing frequency of adenocarcinoma, its lower cost, and the devastating consequences of brain metastases on quality-of-life. As for locoregional staging, it was mentioned that the overall accuracy of CT scan in lymph node is only 60%, and that

mediastinoscopy should play an essential role in patients suspected of locally advanced NSCLC, both within or outside clinical trials. Positron emission tomography (PET) may prove superior, but is not yet universally available. *Mediastinoscopy plays an essential role in the locoregional staging of non-small cell lung cancer, both in and outside clinical trials. PET scan will probably be of further benefit, but is not yet readily available.*

Historical comparators: locoregional therapy alone

Except for the two situations mentioned above, the treatment results of either surgery or radiotherapy alone in stage III NSCLC have been dismal. If patients with positive mediastinal nodes found at mediastinoscopy are treated with surgery plus mediastinal dissection or radical radiotherapy, only 5 to 10% of the patients will achieve a 5-year survival.

Chemotherapy plus radiotherapy in stage III NSCLC

Noah C. Choi (Boston, US) commented on several studies, which have now confirmed the superiority of a combination of cisplatin based chemotherapy with radiotherapy over radiotherapy alone in the treatment of stage III NSCLC. This can be attributed to better control of distant micrometastatic disease and maybe to better local control. In the series of Le Chevalier et al. (J Natl Cancer Inst 83:417,1993) the development of distant metastases was reduced from 70% in the radiotherapy arm to 49% in the combined chemoradiotherapy arm. A survival advantage was found both in series using a sequential or a concurrent approach. A study reported at ASCO 1997 by Furuse et al. suggested a survival benefit for concurrent mitomycin-vindesine-platinum chemotherapy plus 56 Gy radiotherapy over the sequential approach.

There is definitive evidence that cisplatin based chemotherapy combined with radiotherapy is superior to radiotherapy alone in stage III non-small cell lung cancer. The precise timing and scheduling of both modalities remains under investigation.

Induction chemotherapy followed by surgery in stage III NSCLC

If the addition of cisplatin based chemotherapy is beneficial when added to radiotherapy, an other logical option is to use induction chemotherapy before surgery. Several non-controlled phase II studies, enrolling mediastinoscopy positive patients, have shown responses to cisplatin chemotherapy of 60 to 70%, median survival times ranging from 15 to 19 months, and 5-year survival rates of 17 to 19%, clearly better results than in historical series. Randomised studies on this issue are grossly underpowered and several legitimate criticisms can be made. Nonetheless, two of these studies show a significant survival benefit for the combined chemotherapy plus surgery approach.

Induction chemoradiotherapy followed by surgery in stage III NSCLC

The approach of concurrent chemo- and radiotherapy induction has the theoretical advantage of synergy between both induction modalities, which can be delivered in a short delay. Median survival times in non-controlled phase II studies using this approach range from 13 to 23 months, with reported survival rates at 5 years between 22 and 37%. This may seem somewhat higher than in the chemotherapy induction data. The chairman emphasised that much of the difference probably can be explained by more stringent patient selection. The toxicity of chemoradiation is indeed higher, with higher surgical morbidity, and this may be reflected in investigators choosing more fit patients for the chemoradiation approach.

In an attempt to improve locoregional control, new schedules combining chemotherapy and radiotherapy are under investigation. Choi commented on his preoperative chemoradiotherapy schedule using a BID radiation. The BID fractionation has the theoretical advantages of enhancement of tumour response, increase in overall dose-intensity, and sparing of normal tissues. With this approach, a 5-year survival rate of 37% was obtained in stage IIIA-N2 patients. Grade 4 neutropenia (14%), hospital admission for infection (9%), and grade 4 dysphagia (14%) were the most important toxicities. There were 3 treatment related deaths.

Is surgery needed in combined modality approaches in stage III NSCLC?

Although surgery is the therapy most often associated with cure in early NSCLC, comparison of treatment results in stage III patients shows a 5-year survival of 17 to 37% for chemotherapy followed by surgery, versus 6 to 23% for non-surgical combined strategies. One must keep in mind that the more fit patients will usually have the surgical approach in non-controlled trials, and that a substantially higher proportion of stage IIIB patients are included in non-surgical series.

An argument for surgery could be the high (up to 80%) local relapse rate in patients treated with chemoradiotherapy. Pathologic examination of resection specimens after induction chemotherapy or chemoradiotherapy, show that few patients (5 to 15%) have a pathologic complete response. Several important prospective trials, both in the US (RTOG) and Europe (EORTC) are currently examining the role of surgery in the combined approach of stage III NSCLC.

Whether the addition of surgery in the combined modality treatment of stage III non-small cell lung cancer will ultimately improve the therapeutic outcome, remains to be defined. A US and European trial are underway to address this question. One of the advantages of a surgical approach, is the availability of pathologic examination of the resection specimen, which allows a more detailed comparison of different induction regimens.

IIIA versus IIIB disease

A few non-controlled series concentrated on patients with IIIB disease, and suggested that some patients might do well with trimodality treatment. Detailed analysis of these studies shows that the long-term survivors are mostly found in the patients with a T4 disease, and perhaps in patients with upper lobe tumours with ipsilateral supraclavicular lymph node metastases. Cure in patients with contralateral lymph node metastases is very rare, and they should be treated with a non-surgical approach, except in well designed clinical trials.

Outside well-defined investigational protocols, stage IIIB remains a non-surgical disease.

Conclusions and perspectives: Is cure of 50% of the stage IIIA patients a goal for the next decade?

A staging strategy as stringent as possible must define patient groups: thorough locoregional staging with mediastinoscopy, a complete metastatic work-up, and probably an increasing role of PET scan.

In the last decade, a fascinating evolution has taken place, bringing chances for long-term remission or 5-year survival to patients, who previously were considered to be incurable. Our standard cisplatin based induction chemotherapy is now able to produce 5 to 15% of pathologic complete responses. Combined with appropriate and radical locoregional therapy and/or surgery, this probably allows to cure 25 to 30% of these patients. Current therapeutic options in stage III disease are outlined in table 2.

In the next decade promising new agents (docetaxel, gemcitabine, vinorelbine, paclitaxel,...), especially if combined with cisplatin, will probably improve the number of pathologic complete responses, and hopefully also the long-term survival results. To reach the 50% 5-year survival barrier, however, other modalities will probably be needed, e.g. to eliminate minimal residual disease. Interesting options are front-line approaches such as anti-angiogenesis agents, tumour vaccines, monoclonal antibodies, antisense oligonucleotides, and gene replacement therapy.

Further improvement in stage III non-small cell lung therapeutic results is to be expected from more effective induction regimens including newer agents, and the addition of biological disease modifying strategies in the future.

Non-small cell lung cancer (NSCLC) session 1998

Sandler (Indianapolis, US), presented an interim report on 309 patients enrolled in a randomised study comparing cisplatin (100 mg/m², day 1, q 4 weeks) with or without gemcitabine (1000 mg/m², days 1, 8 and 15, q 4 weeks). As could be expected, response rate, time to progression and survival were better in the cisplatin-gemcitabine arm. Although haematologic toxicity was more important in the combination arm, it is worth mentioning that non-haematological toxicity did *not* increase when the combination was compared with cisplatin alone.

Crino (Perugia, Italy) showed the results of a randomised trial comparing the mitomycin-ifosfamide-cisplatin (MIC) regimen with cisplatin (100 mg/m², day 2, q 4 weeks) and gemcitabine (1000 mg/m², days 1, 8 and 15, q 4 weeks). Overall response rate was better in the cisplatin-gemcitabine arm (40%) than in the MIC arm (28%; P=0.03). Median survival time was not different between both arms. Myelosuppression was the main toxicity in both arms, with more grade 3-4 thrombocytopenia for cisplatin-gemcitabine. Non-haematological toxicity was mild.

Van Zandwijk (Amsterdam, Holland) presented a poster with the first results of cisplatin-gemcitabine as induction regimen in 36 stage IIIA patients. The response rate after 3 cycles of this induction schedule was as high as 77%.

The response rate of the cisplatin-gemcitabine combination proved to be 40% in a phase III randomised study, compared to 28% with a standard cisplatin based schedule. The combination also seemed very active in the first EORTC data in stage IIIA patients.

Gatzemeier (Grosshansdorf, Germany) reported on a randomised comparative study of 414 patients treated with either 100 mg/m² cisplatin monotherapy, or taxol 175 mg/m² over 3 hours followed by 80 mg/m² cisplatin. Although the response rate **was** a little higher in the combination arm, median survival times were equivalent: 8.6 months for cisplatin versus 8.1 months for cisplatin-taxol. A borderline difference in quality of life in favour of cisplatin-taxol was noted.

The most remarkable presentation was brought by **Belani** (Pittsburgh, US). A North-American inter-group study compared standard cisplatin (75 mg/m²) plus etoposide (100 mg/m², days 1, 2 and 3) on the one hand with carboplatin AUC=6 plus taxol 225 mg/m² over 3 hours on the other. Three hundred and sixty-nine patients were randomised. The response rate was slightly better for carboplatin-taxol than for cisplatin-etoposide. Median survival time and 1-year survival were not different. In patients receiving more than 3 cycles, there was a significantly higher occurrence of grade 3-4 neuropathy in the carboplatin-taxol arm (24 patients) than in the cisplatin-etoposide arm (1 patient; P<0.001). Quality of life during the first 3 cycles was slightly better for carboplatin-taxol.

These new data were put into perspective by **Shepherd** (Toronto, Canada). At the 1995 ASCO meeting, phase II data on the carboplatin-taxol combination were reported, suggesting a response rate of 62% and a 1-year survival of 54%. In later phase III data, these results fell to a 27% response rate, and a 32% 1-year survival. In the current data of Belani et al., response rate was a mere 21%, with no difference at all in median or 1-year survival when compared with the older cisplatin-etoposide regimen. Moreover, the current presentation by Gatzemeier et al. did not suggest a clear superiority of cisplatin-taxol over cisplatin alone.

In contrast with early phase II data at ASCO 1995, very sobering data on the carboplatin-taxol combination were now reported. No difference in survival could be demonstrated compared to the cisplatin-etoposide regimen, a standard combination dating from the 1980's and about 7 times less expensive.

On behalf of the CATAPULT-I study group, **Von Pawel** (Gauting, Germany) reported on a randomised trial comparing cisplatin plus tirapazamine with cisplatin alone. Tirapazamine is a new bioreductor active against hypoxic cells, amongst others by selective sensitisation of hypoxic cells to cisplatin. Response rate was higher in the tirapazamine arm (27 versus 14%; P<0.001), and median survival was better (35 versus 28 weeks; P=0.0078). Tirapazamine was responsible for manageable muscle cramping, but did not cause additional myelosuppression.

Stewart from the MRC Cancer Trials Office (Cambridge, UK) presented a meta-analysis on the role of postoperative radiotherapy in NSCLC. Individual data from 2128 patients were taken into account. Postoperative radiotherapy caused a 22% increase in the risk of death, equivalent to a 7% decrease in 2-year survival results (from 55 to 48%). The detrimental effect of postoperative irradiation was more pronounced in stages I and II.

Individual randomised trials on the use of postoperative radiotherapy in resected NSCLC have never shown a survival benefit. In a recent meta-analysis, an unfavourable effect on survival was found with 7% reduction in 2-year survival.

Table 1 : Evaluation of the patient with suspected stage III NSCLC

Clinical evaluation

- History and physical examination
- Performance status
- Routine lab tests

Radiographic evaluation

- Chest X-ray
- Chest CT scan (including liver/adrenals)
- Cranial CT or MRI

Bone scan (if symptoms or **raised** alkaline phosphatase)

- PET scan if available
- Pulmonary evaluation
- Bronchoscopy
 - Pulmonary function tests including DLCO
 - Quantitative perfusion scan (if compromised pulmonary function)
- Surgical staging
- Mediastinoscopy
 - Anterior mediastinotomy or thoracoscopy (if left upper lobe tumour)

Table 2 : Treatment options in stage III NSCLC

Single modality : surgery (postoperative chemotherapy under study)

- Resectable T3 tumours
- Unforeseen N2 (i.e. after negative mediastinoscopy)

Combined modality in stage IIIA-N2 (positive mediastinoscopy)

- Chemoradiotherapy
- Induction followed by surgery
 - chemotherapy induction
 - chemoradiotherapy induction
- Induction chemotherapy followed by chemoradiation

Combined modality in stage IIIB

- Caused by T4 : chemoradiotherapy (maybe plus surgery)
- Caused by N3 : chemoradiotherapy

Small cell lung cancer (SCLC) session 1998

Thatcher from the MRC Cancer Trials Office (Cambridge, UK) presented a randomised trial on dose intensification in SCLC. Six cycles of ACE chemotherapy were administered every 3 **weeks** in one arm (conventional dose arm, CD), every 2 **weeks** with G-CSF support from day 4 to 14 in the other (dose increase arm, DI). ACE consisted of adriamycin 40 mg/m² IV, cyclophosphamide 1000 mg/m² IV, and etoposide 120 mg/m² IV on day 1 plus 240 mg/m² orally on days 2 and 3. Despite G-CSF support, only 63% of the patients in the DI arm received their second cycle on time, and this fell to 58%, 47%, 36% and 33% for the subsequent cycles. The mean reason for delay in the DI arm was thrombocytopenia. A dose increase of 33%, instead of the planned 50%, was obtained. Response rates were similar. There was a slight reduction in tumour related death in the DI arm (hazard ratio 0.80, 95% C.I. 0.65-0.99; P=0.04), resulting in a small difference in 1-year survival (47% for DI versus 39% for CD).

Use of G-CSF did not allow a planned dose increase of 50% of adriamycin-cyclophosphamide-etoposide chemotherapy, mainly due to increased thrombocytopenia. Thirty-three percent dose increase could be obtained, resulting in a minor survival benefit.

Schiller (Wisconsin, US) presented a randomised multicentre study comparing topotecan and CAV in SCLC sensitive relapse (that is occurring more than **90** days after cessation of first line therapy). Topotecan was given at a dose level of 1.5 mg/m² during 5 days, every 3 **weeks**. CAV consisted of cyclophosphamide 1000 mg/m², adriamycin 45 mg/m² and vincristine 2 mg/m², administered every 3 week. Response rates were 24% for topotecan and 17% for CAV. There was no significant difference in median response duration, time to progression or survival. Grade 4 thrombocytopenia was more frequent with topotecan (29 versus 5%; P<0.001). Several symptoms of disease were longer controlled with topotecan.

Single agent topotecan is comparable to CAV in the treatment of sensitive relapse of SCLC, but a 5 day schedule of administration is needed. It appeared to offer somewhat better palliation of disease symptoms than CAV.

A better integration of chemotherapy and radiotherapy is expected to improve the therapeutic outcome in limited disease SCLC.

Turrisi (Charleston, US) reported the 5-year follow-up findings in North-American trials comparing radiotherapy concurrent with cisplatin-etoposide chemotherapy, delivered in either daily (QD) or twice daily (BID) fractionation. Survival data were clearly superior for the BID radiotherapy: 2-year survival 46 versus 41%, and 5-year survival 26 versus 16% (P=0.043). This could probably be attributed to reduction of local failure in the **BID** arm: the incidence of local failure alone was 36% after BID and 52% after QD radiotherapy (P=0.058).

Arriagada (Paris, France) presented a meta-analysis on the role of prophylactic cranial irradiation in patients with SCLC in complete remission. It is well known that prophylactic cranial irradiation reduces the occurrence of brain metastases, but an effect on survival could never be demonstrated in individual trials. In the current meta-analysis, individual data on 987 patients were analysed. The relative risk of death was reduced by prophylactic cranial irradiation to 0.84 (95% C.I. 0.73-0.97; P=0.01). This resulted in a 5.4% increase in the 3-year survival rate from 15.3 to 20.7%. The effect on survival did not seem to be dependent of the administered radiotherapy schedule or dose.

*Better integration of chemotherapy and radiotherapy resulted in improved survival in limited disease SCLC. North-American 5-year survival data showed an advantage for **concurrent BID** thoracic irradiation over standard once daily schedules. A meta-analysis showed a beneficial effect on survival of prophylactic cranial irradiation in patients **with** a complete response.*