Expanding role of chemotherapy in lung cancer

Y. Loriot¹, J.-C. Soria¹ & T. Le Chevalier¹,²

¹Department of Medicine, Institut Gustave-Roussy, Villejuif ²Institut National du Cancer, Paris, France

introduction

Lung cancer is a major cause of mortality worldwide, with an estimated annual incidence of over 1.2 million cases and overall mortality of over 1.1 million cases [1]. In the United States alone in 2003, an estimated 171 900 new cases of lung cancer will be diagnosed, and this disease will cause an estimated 157 200 deaths [2]. Estimates of cancer incidence and mortality in Europe in 2000 predicted 375 000 new cases of lung cancer and 347 000 deaths due to this disease [3]. In Europe, the mortality rates are rising in women, due to the increasing tobacco use [4]. The overall 5-year survival rates of patients with lung cancer have only modestly increased over the last 25 years, remaining at approximately 14% [5]. This disappointing figure may have several explanations including age at diagnosis (median 69 years), the high frequency of co-morbidities, and the absence of significantly relevant improvement of the three major therapeutic modalities, i.e. surgery, radiotherapy and chemotherapy. Nevertheless, the emergence of some new drugs and concepts has broadened the perspectives of lung cancer management.

chemotherapy and metastatic disease

evidence of interest for chemotherapy in metastatic disease

In the setting of lung cancer, non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung tumors. Approximately half of the patients present with metastatic disease. In addition, a majority of patients with limited disease at diagnosis will experience a later dissemination, so that eventually more than 80% of patients with NSCLC require a systemic treatment during the course of their disease. The outcome of untreated patients with advanced NSCLC is predictable with a median survival time of 4 months, and a 1-year survival rate of 10 to 15%. In the MRC-IGR meta-analysis, a total of 1190 patients with advanced disease were included and the results suggested that cisplatin-based chemotherapy offered a 27% reduction in the risk of death (p<0.0001), an improvement of median survival of 6 weeks and an improvement of survival of 10% at one year [6]. Furthermore, most studies that have evaluated the quality of life of patients reported a subjective improvement associated with the prolongation of life [7]. Even if the benefit is modest, most physicians and patients agree to consider chemotherapy as the standard treatment of patients with advanced NSCLC, at least for those with adequate performance status and age.

the old combinations or the new combinations?

With a response rate of 20%, cisplatin has been considered the key-drug in the treatment of NSCLC, since 1980 and the combination of cisplatin-etoposide, cisplatin-vinblastine and cisplatin-vindesine have been considered standard regimens for NSCLC up to the mid-1990s. In the last ten years, several new cytotoxic agents have become available; these include the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine and the topoisomerase 1 inhibitor irinotecan. Some of these new drugs were compared to the best supportive care or to older drugs in randomized studies [8, 9]. They were also compared to old doublets and generally demonstrated an attractive activity/toxicity profile [10, 11]. Randomized trials comparing new combination regimens with older platinum-based doublets underline the greater possibilities that the new agents can offer [10, 12–14].

is there a better doublet?

In the recent past, several randomized studies were dedicated to the comparison of these new doublets. They showed no significant or relevant differences among these doublets as seen in Table 1. The ECOG 1594 study compared cisplatin-paclitaxel/24-hour with cisplatin-docetaxel, cisplatin-gemcitabine, or carboplatin-paclitaxel/3-hour and no survival differences were showed among the four treatment arms [15].

The South West Oncology Group (SWOG) conducted a randomized phase III trial comparing paclitaxel-carboplatin to the SWOG standard vinorelbine-cisplatin [16]. Both regimens gave results comparable to those observed in ECOG 1594. Within SWOG 9509, the two regimens were equally effective both in terms of response and survival. The Italian Lung Cancer Study Group compared cisplatin-gemcitabine versus paclitaxel-carboplatin versus cisplatin-vinorelbine in untreated patients with locally advanced or metastatic NSCLC [17]. This study failed to demonstrate a therapeutic advantage of any of these three regimens in terms of survival or response and this result is entirely consistent with the results of the ECOG and SWOG trials, providing further evidence that all these regimens remain reasonable choices for patients with advanced NSCLC.

cisplatin or carboplatin?

Because cisplatin has significant toxicities including severe nausea and vomiting, renal toxicity requiring adequate hydration, ototoxicity and neuropathy, platinum-analogs have been developed. Among them, carboplatin, which was
introduced in clinical trials in the early 1980s, is still the leading compound. Carboplatin-based chemotherapy in patients with locally advanced and metastatic NSCLC has been widely used, particularly in the United States, as an alternative to cisplatin-based chemotherapy in order to minimize clinical toxicities [18]. Most previous studies suggest no clear difference and generally a better tolerance and comfort with carboplatin [15, 16]. Nevertheless, a recent European study questions the equivalence of the two platinum compounds [19]. In this study, 618 patients were randomized to receive paclitaxel 200 mg/m² in combination with either carboplatin at an area under the curve (AUC) of 6 or cisplatin at 80 mg/m² every 3 weeks. A survival update after 22 months of additional follow-up yielded a median survival of 8.2 months in the paclitaxel/carboplatin arm and 9.8 months in the paclitaxel/cisplatin arm [hazard ratio = 1.22, 90% CI: 1.06–1.40; P = 0.019]; the 2-year survival rates were 9% and 15%, respectively. Excluding neutropenia and thrombocytopenia, which were more frequent in the paclitaxel/carboplatin arm, and nausea/vomiting and nephrotoxicity, which were more frequent in the paclitaxel/cisplatin arm, the rate of severe toxicities was generally low and equivalent between the two arms. The preliminary results of TAX 326, in which docetaxel was combined with either cisplatin or carboplatin in the two investigational arms, go along the same lines [20]. Thus carboplatin might not possess equivalent activity to cisplatin in the setting of lung cancer. If patients with NSCLC requiring chemotherapy have contraindications to the use of cisplatin such as inability to receive hyperhydration (cardiac dysfunction, superior vena cava syndrome) or previous neurological or hearing problems, carboplatin is an appropriate alternative to cisplatin in 2006.

are triplets more active than doublets?
There is a rationale to propose the combination of three cytotoxic agents in the treatment of solid malignancies. This is based on preclinical data suggesting a synergistic activity between drugs with different mechanism of action and the possibility of delivering lower doses of each drug without decreasing the anti-tumor effect or increasing the toxicity of the combination. Unfortunately, in spite of encouraging response rates in phase II studies, most triplets failed to demonstrate superiority over standard doublets. Two recent randomized studies compared the gemcitabine-cisplatin standard doublet to the combination of gemcitabine-vinorelbine-cisplatin [21, 22]. Results of these two trials were provocatively different as seen in Table 2. A recent literature-based meta-analysis confirmed the lack of significant impact of triplets over doublets in advanced NSCLC [23] and the use of 3-drug combinations remains investigational and of unproven benefit at the present time.

second-line chemotherapy
Improvement of response and survival obtained with current chemotherapy regimens have led to the development of second-line treatments, which have become an important issue for patients whose disease progresses after receiving front-line chemotherapy. Response rates to single agents such as vindesine, etoposide, epirubicin and cisplatin have not exceeded 10% in second-line treatment. The new generation of cytotoxic agents seem more active with response rates ranging from 0% to 23% in several phase II studies. Among these drugs, docetaxel was the most promising with a response rate of approximately 15%. Phase II data led to two large phase III randomized trials in which single agent docetaxel was compared with best supportive care or ifosfamide or vinorelbine in patients having failed cisplatin-based first-line chemotherapy [28, 29]. Both studies demonstrated the superiority of docetaxel over the comparator and a better quality of life with docetaxel given at 75 mg/m² every three weeks. Pemetrexed, a multi-targeted anti-folate, has shown activity in second-line chemotherapy [30]. A randomized study comparing pemetrexed to docetaxel in second-line chemotherapy drug fee) for group A (Euro; 7612.64) versus group B (Euro; 7484.77) was not statistically significant (P < 0.66). Other randomized trials confirmed the equivalence between platinum-free and platinum-based regimens [25–27].

Table 1. Randomized phase III trials comparing different modern doublets (Experience of SWOG, ECOG and Italian group)

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>n</th>
<th>OR</th>
<th>MS (months)</th>
<th>1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine+Cisplatin [16]</td>
<td>207</td>
<td>27</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>Paclitaxel+Carboplatin [16]</td>
<td>201</td>
<td>27</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>Paclitaxel+Cisplatin [15]</td>
<td>299</td>
<td>15</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Gemcitabine+Cisplatin [15]</td>
<td>301</td>
<td>21</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>Docetaxel+Cisplatin [15]</td>
<td>304</td>
<td>17</td>
<td>7.5</td>
<td>31</td>
</tr>
<tr>
<td>Paclitaxel+Cisplatin [17]</td>
<td>201</td>
<td>32</td>
<td>9</td>
<td>43</td>
</tr>
<tr>
<td>Gemcitabine+cisplatin [17]</td>
<td>205</td>
<td>30</td>
<td>9</td>
<td>37</td>
</tr>
<tr>
<td>Vinorelbine+Cisplatin [17]</td>
<td>201</td>
<td>30</td>
<td>9</td>
<td>37</td>
</tr>
</tbody>
</table>

OR, objective response; MS, median survival.

Table 2. Comparison of gemcitabine-cisplatin (GC) and gemcitabine-vinorelbine-cisplatin (GVC)

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>n</th>
<th>GC (Comella)</th>
<th>Alberola [22]</th>
<th>GVC (Comella)</th>
<th>Alberola [22]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>28%</td>
<td>41%</td>
<td>44%</td>
<td>40%</td>
</tr>
<tr>
<td>MS (w)</td>
<td>38</td>
<td>40.8</td>
<td>51</td>
<td>34.4</td>
<td>38</td>
</tr>
</tbody>
</table>

OR, objective response; MS, median survival; w, weeks.
treatment has recently shown the equivalence between the two drugs (median survival of 8.3 months and 7.9 months respectively) [31]. In treatment after second-line failure, the role of chemotherapy is less clear [32].

**chemotherapy in elderly patients**

Sixty per cent of patients with NSCLC are over 65 years and chemotherapy is being questioned in these patients since comorbidities are likely to increase chemotherapy-associated toxicity. Monotherapy has been evaluated in order to limit adverse events. A randomized phase III trial has demonstrated a benefit of vinorelbine associated with best supportive care in comparison with best supportive care (1 year survival of 32% versus 14%) [33]. A second phase III study compared the combination of vinorelbine (30 mg/m² days 1 and 8 every 3 weeks) and gemcitabine (1200 mg/m²) with vinorelbine alone and showed a better 1-year survival in the combination arm (30% versus 13% respectively) [34]. However a larger trial which compared the association of vinorelbine (25 mg/m² days 1 and 8 every 3 weeks) and gemcitabine (1000 mg/m² day 1) with either vinorelbine alone (30 mg/m²) or gemcitabine (1200 mg/m²) alone on days 1 and 8 every three weeks. The results have not found any benefit for overall survival and the toxicity was more important in the combination arm [35]. No prospective data from phase III trials are available about the role of platinum-based chemotherapy in elderly patients. A retrospective analysis of elderly patients included in large phase III trials showed no significant differences between elderly and younger patients in either response rate or overall survival but a small increase of toxicity in elderly patients [36].

**tailored chemotherapy**

A rationale and treatment decision-making process based on the analysis of biomarkers of response and resistance to cytotoxic drugs appears to be a major issue for the next future. At present, research on cancer survival is partly focused on translational pharmacogenomics, aimed at providing individualized chemotherapy based on genetic traits, such as polymorphisms, gene mutations, and overexpression of drug-targeted gene transcripts. Cisplatin has long been the scaffolding of chemotherapy in lung cancer. Like many DNA alkylators, cisplatin acts as a cross-linker, inhibiting DNA replication, which is the critical target in cancer chemotherapy. Cross-links between guanine bases are induced by cisplatin, carboplatin and oxalipatin. There are several major DNA repair pathways. Excision repair, including nucleotide excision repair (NER) has been strongly linked to cisplatin resistance. Excision repair cross complementation group-1 (ERCC1) is a key gene on the NER pathway. A growing list of reports link cisplatin, carboplatin and oxalipatin resistance to ERCC1 mRNA expression. This relationship has been suggested for gastric cancer patients, ovarian cancer patients, colorectal cancer patients and more recently for non-small cell lung cancer patients [37–40]. Ribonucleotide reductase (RR) is the rate-limiting enzyme of the DNA synthesis pathway and converts ribonucleoside diphosphate to deoxyribonucleoside diphosphate, which is essential for DNA synthesis and repair. RR consists of two subunits, M1 and M2. The M1 subunit controls substrate specificity and global on/off enzyme activity, while the M2 subunit carries the catalytic domain responsible for substrate conversion. RRM1 also acts as a putative tumor suppressor and has been identified within the centromeric part of chromosome segment 11p15.5. This region, called LOH11A, is frequently lost in NSCLC. Loss of heterozygosity in this region has been shown to be highly predictive of poor survival in patients with resected NSCLC patients [41]. Along the same lines, overexpression of RR indicates resistance to gemcitabine in the human KB cancer cell line [42]. Recently, it has been shown that flavopiridol downregulates the ribonucleotide reductase M2 subunit, supporting the concept that this enzyme could become a relevant biomarker for gemcitabine response [43]. Gemcitabine is a hydrophobic compound and its cellular penetration is partly ensured by the transport membrane protein hENT1 (equilibrative nucleoside transporter). It has been demonstrated that deficiency in hENT1 confers high-level resistance to gemcitabine toxicity in vitro [44]. Microtubules are cytoskeletal protein polymers that present a large protein surface in the cell. Microtubules are polymers built by the self-association of α/β-tubulin dimers and are critical for cell growth and division, motility and signaling. Recently, beta-tubulin (HM40) mutations have been described in vincristine-resistant acute leukemia [45]. Previously, β-tubulin mutations had been identified in ovarian and lung cancer patients who were resistant either to paclitaxel or epiphilone [45]. However, it seems that multiple microtubule alterations could be involved in the mechanisms of this resistance, including up- or down-regulation of several transcripts. The level of class III beta-tubulin (Hβ4) isotype in a cell can affect its response to paclitaxel. Antisense oligonucleotides targeting class III β-tubulin led to a 39% increase in sensitivity to paclitaxel in resistant lung cancer cells A549-T24 [46, 47]. Quantitative polymerase chain reaction (PCR) showed a significant correlation between increased expression of class III β-tubulin isotype and paclitaxel resistance in human ovarian carcinoma xenografts [48]. Nucleotide polymorphisms are one of the most frequent changes that can be found in gene sequences. Polymorphisms can disclose the underlying host factors that explain inter-individual differences in treatment efficacy. XPD (excision repair cross complementing group 2) is involved in the nucleotide excision repair pathway, like ERCC1. XPD polymorphisms can modulate the effect of the DNA repair capacity. In this respect, the variant Lys 751Gln and Asp312Asn homozygous alleles show a suboptimal DNA repair capacity in lung cancer patients in comparison with controls with wild-type genotypes. This raises the hypothesis that variants of these polymorphisms could be sensors of cisplatin chemosensitivity [49]. XRCC1 plays a central role in the base excision repair process. Recently, a polymorphism in exon 10 (Arg–Gln, codon 399) has been detected. Colorectal cancer patients who responded to oxalipatin had an Arg/Arg genotype, while non-responders were homozygous for the variant Gln/Gln or heterozygous for Gln/Arg [50].

**targeted agents**

The better understanding of the biology of lung cancer has led to the development of novel therapies directed at tumor-specific
targets. Most of these targets are tumor growth factor signal pathways but tumor proliferation, angiogenesis or apoptosis may also be targeted, particularly by targeting the epidermal growth factor receptor (EGFR) pathway since overexpression of EGFR is found in NSCLC. Erlotinib and gefitinib inhibit the tyrosine kinase activity of EGFR and have been extensively evaluated in NSCLC [51–54]. Recently, a randomized phase III proved a benefit of survival for erlotinib compared with placebo in patients with previously treated NSCLC (overall survival 6.7 and 4.7 months respectively, hazard ratio 0.70; P <0.001) [55]. Among patients with NSCLC who receive erlotinib, the presence of an EGFR mutation may increase responsiveness to the agent, but it is not indicative of a survival benefit [56]. Nevertheless, the combination of cytotoxic doublets combined with EGFR inhibitors have failed to demonstrate any substantial benefit in phase III trials [57–60].

More recently, the Eastern Cooperative Oncology Group (ECOG) reported the results of a randomized trial in 878 patients with chemo-naive inoperable NSCLC, which evaluated the effectiveness of the addition of bevacizumab, an anti-angiogenic agent, to the standard paclitaxel-carboplatin combination. Median survival was significantly increased in the bevacizumab arm (12.5 months versus 10.2 months; P = 0.0075) [61]. This trial is the first one showing that the addition of a targeted agent to a standard cytotoxic doublet could prolong survival. Further investigations are expected in the near future.

**Chemotherapy and locally advanced disease**

At diagnosis, approximately 25% of patients with NSCLC have locally advanced disease and are thus considered as unresectable (stage IIIb). For the past 10 years, combined treatment has become the standard, particularly for those patients with good general condition and younger than 70 years. Both modalities may be given either sequentially or simultaneously. Many studies have explored the impact of the addition of chemotherapy (CT) to radiotherapy (RT) sequentially. The meta-analysis on 3033 patients from 22 randomized trials, comparing radiotherapy alone and radiotherapy combined with chemotherapy, showed a significant benefit of cisplatin-based chemotherapy with either sequential or concurrent radiotherapy, with a 10% reduction in the risk of death corresponding to an absolute survival benefit of 3% at 2 years and 2% at 5 years [6]. The final results of the phase III RTOG study confirmed the modest benefit of a sequential treatment over radiotherapy alone [62].

Another possibility to combine chemotherapy and radiotherapy is to give them simultaneously. Several phase III trials comparing concomitant chemoradiation to radiotherapy alone failed to demonstrate any benefit of concurrent chemoradiation over radiotherapy alone but used sub-optimal doses with radiosensitizing properties [63] whereas few trials suggested a benefit of this concurrent approach [64]. Because of these disappointing results of radiosensitizing chemotherapy, concurrent chemotherapies with cytotoxic doses were developed.

A Japanese group conducted a phase III study comparing concurrent versus sequential radiotherapy [65]. Concomitant chemoradiation produced a higher response rate (84% versus 66%), and a significant survival advantage (P = 0.04) with a median survival of 16.5 months versus 13.3 months in the sequential arm. An analysis of patterns of recurrence showed that prolonged survival was associated with a better intrathoracic tumor control in the concomitant arm. The RTOG also conducted a phase III study comparing concurrent versus sequential chemoradiation with cisplatin and vindesine in 611 patients with stage II and III NSCLC [66]. The results demonstrated a significant improvement in median survival with concurrent once-daily chemoradiation, compared to the sequential approach (17 months versus 14.6 months, P = 0.038). Survival was not statistically improved for patients with twice-daily radiotherapy compared with the standard fractionation (median survival of 15.6 months, P = 0.55).

Another study compared sequential chemoradiation with cisplatin and vinorelbine followed by thoracic radiation with the same radiotherapy delivered concomitantly with two cycles of cisplatin-etoposide. The overall survival was not significantly different between the two groups (median survival of 13.8 months in the sequential arm and 15 months in the concomitant arm) [67]. These results are summarized in Table 3.

The new drugs have been evaluated with concomitant radiotherapy in stage III disease. In CALGB 9431, 181 stage III patients were randomized to receive cisplatin plus either gemcitabine or paclitaxel or vinorelbine. Radiotherapy was delivered at a dose of 66 Gy [68]. Tolerance was acceptable in all three groups during the induction treatment. The first analysis showed a median survival of 17.2 months in the gemcitabine-cisplatin group, 14.1 months in the paclitaxel-cisplatin group and 17.7 months in the vinorelbine-cisplatin group.

Weekly paclitaxel associated with carboplatin also seems to be an interesting regimen combined with concomitant RT with response rates around 70% and 2-year survival rate of 40% [69, 70].

Induction chemotherapy followed by concurrent chemotherapy has also been evaluated. CALGB evaluated induction paclitaxel (200 mg/m²) and carboplatin (AUC6) before chemoradiation to 66 Gy with weekly carboplatin (AUC 2) and paclitaxel (50 mg/m²) versus immediate chemoradiation alone. The median and 1-year survival did not differ significantly in the induction/concurrent arm (14.0 months versus 11.4 months) [71].

As local control is a major issue in stage III patients, some feasibility studies have tried to include surgery in order to improve local control and overall survival in selected patients. Front-line CT may be followed by concomitant chemoradiation and surgery. Response rate to induction treatment is 50% and

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Survival</th>
<th>Sequential</th>
<th>Concurrent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furuse [65]</td>
<td>314</td>
<td>2-year survival</td>
<td>27.4</td>
<td>34.6</td>
<td>0.04</td>
</tr>
<tr>
<td>RTOG 9410 [66]</td>
<td>611</td>
<td>2-year survival</td>
<td>31</td>
<td>37</td>
<td>0.04</td>
</tr>
<tr>
<td>GLOT/GFPC [67]</td>
<td>207</td>
<td>2-year survival</td>
<td>24</td>
<td>35</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Annals of Oncology

Table 4. Adjuvant trials in non-small cell lung cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Chemotherapy regimens</th>
<th>No. patients (n)</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis 1995 [6]</td>
<td>Various</td>
<td>1384</td>
<td>NS (P = 0.08)</td>
</tr>
<tr>
<td>ALPI-EORTC [70]</td>
<td>MVPx3</td>
<td>1209</td>
<td>NS</td>
</tr>
<tr>
<td>IALT [71]</td>
<td>Cisplatin+etoposide or alkaloid × ¼</td>
<td>1867</td>
<td>4% at 5 years</td>
</tr>
<tr>
<td>BLT [72]</td>
<td>Cisplatin+vincaalkaloid</td>
<td>381</td>
<td>NS</td>
</tr>
<tr>
<td>JBR-10 [73]</td>
<td>Cisplatin+vinorelbine × 4 cycles</td>
<td>482</td>
<td>14% at 5 years</td>
</tr>
<tr>
<td>CALB 9633 [74]</td>
<td>Carboplatin plus paclitaxel</td>
<td>344</td>
<td>12% at 4 years</td>
</tr>
<tr>
<td>Anita [75]</td>
<td>Cisplatin+vinorelbine × 4 cycles</td>
<td>831</td>
<td>8.6% at 5 years</td>
</tr>
<tr>
<td>UFT meta-analysis [76]</td>
<td>UFT for 1–2 years</td>
<td>2,003</td>
<td>7% at 7 years</td>
</tr>
</tbody>
</table>

NS, not significant.

3-year survival around 25% [72]. These encouraging results deserve confirmation in randomized studies.

**Chemotherapy and early stage disease**

For many years, surgery has been the standard treatment for patients with early stage NSCLC. Despite complete resection, 5-year survival rates have been disappointing, ranging from 67% for T1N0 patients to 23% in patients with ipsilateral mediastinal lymph node involvement [73]. Following surgery, distant recurrence is the most common form of relapse and eventual cause of death.

Efforts at improving survival for patients with operable NSCLC have examined the addition of chemotherapy in the preoperative or postoperative settings. In the meta-analysis reported in 1995, 8 trials randomizing a combined total of 1394 patients to a postoperative cisplatin-based combination were examined [6]. The hazard ratio estimates for these eight trials favored chemotherapy. The overall hazard ratio was 0.87 (P = 0.08), corresponding to a 13% reduction in the risk of death, and suggested an absolute benefit from chemotherapy of 3% at 2 years and 5% at 5 years. These findings prompted renewed interest for postoperative chemotherapy in completely resected NSCLC (Table 4). Several reported randomized trials [74–80] are consistent, with overlapping confidence intervals, favoring a beneficial effect of postoperative platinum-based adjuvant chemotherapy. A better definition of those patients more likely to benefit from adjuvant chemotherapy should be obtained with the LACE meta-analysis of these new trials that will be reported shortly.

Another approach is to propose preoperative chemotherapy. If numerous phase II studies have reported promising results in terms of response and resectability, survival benefit has generally been less convincing. In stage IIIA disease, two small randomized trials including 60 patients each reported a significant benefit from preoperative chemotherapy in stage III NSCLC [81, 82].

A large multicentre trial performed in France [83] in 373 patients also suggested a benefit but the difference did not reach a significant level.

New randomized trials have recently been completed or are ongoing in Europe and North America. They question the impact of neo-adjuvant chemotherapy in early stage NSCLC, the benefit of new regimens in terms of activity and toxicity and the number of cycles to be given preoperatively.

**Conclusion**

Chemotherapy has become a key treatment for advanced NSCLC in the last decade. Several new cytotoxic agents have been proven superior to older agents even if the statistically significant benefit observed remains modest in terms of survival impact. The new combinations are generally more active and better tolerated than the old one. Tailored chemotherapy and new targeted treatments are being presently explored. The addition of concomitant chemotherapy to radiotherapy increases survival for locally advanced cancer. The benefit of adjuvant chemotherapy for resectable NSCLC is clearly proven.

**References**


