Management of small-cell lung cancer

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Introduction

Cancer mortality in Europe, after a long-term increase, has actually fallen in recent years [1]. Although there was an 11% fall in lung cancer mortality in men in the European Union, there was an increase in women of 15% [2]. Lung cancer mortality rates remain highest for males in Hungary, Croatia, Poland, Belgium and the Russian Federation, and for women in Scotland, Denmark, Iceland, Hungary, England and Wales. An overview of trends since 1960 has shown a fall or levelling off of lung cancer mortality for men in the last decade in most countries except Portugal and Romania. Unfortunately, for women a general upward trend has been noted except in Denmark, Iceland, Ireland and the UK, with an actual fall in the Russian Federation [1]. Lung cancer will continue to be the major cancer problem in Europe for several decades to come unless more effective tobacco control is instituted [1]. Furthermore, there has been a decrease in the proportion of lung cancer patients with small-cell lung cancer (SCLC), currently ~14% in the USA [3].

Prognostic groups

In SCLC, tumour extent is defined as extensive (ES) or limited (LS) stage disease. LS (present in ~30% of SCLC patients) is tumour confined to one hemithorax including the mediastinum, i.e. contained within a single radiation field. LS has also included in some studies ipsilateral pleural effusions, and supraclavicular and contralateral regional nodes. ES disease is more widespread tumour. Moreover, there are a number of other independent prognostic factors that predict survival including performance status (PS) and biochemical indices, e.g. lactate dehydrogenase, alkaline phosphatase and serum sodium [4–6]. It is important to note that age is not a consistent independent prognostic factor. It is possible to have LS patients with abnormal biochemistry and impaired PS whose prognosis is similar or even less than ES patients of good PS and normal biochemistry; conversely some ES patients may have a similar survival to poorer prognosis LS patients. Independent prognostic factors should be taken into account when determining treatment strategy, e.g. aiming for long-term survival in better prognosis patients, or palliation with improvement in short-term survival in others, thereby avoiding under- or over-treatment. Risk factors for early (treatment-related) death, including impaired PS or abnormal liver function tests, should also be considered in the treatment plan [7, 8].

Chemotherapy overview

Chemotherapy (CT) is the cornerstone of treatment of SCLC, and frequently used drugs include cisplatin, carboplatin, etoposide, cyclophosphamide, ifosfamide, doxorubicin, vincristine and, more recently, topotecan, irinotecan and paclitaxel. Commonly used combinations include: cisplatin or carboplatin plus etoposide (PE or CbE); ifosphamide, carboplatin and etoposide with or without vincristine (ICE±V); cyclophosphamide, doxorubicin and vincristine (CAV); or cyclophosphamide, doxorubicin and etoposide (CDE). Doxorubicin combinations were until recently more commonly given in Europe, but platinum–etoposide regimens are now increasingly used. The median, 2- and 5-year survival for LS is 14–20 months, 20–40% and ~10%, respectively. The median survival for ES is 7–10 months, but survival after 2 years is rare (<5%). However, in less selected groups of patients the overall survival is <5% at 3–5 years [3, 9, 10].

Combination CT is routinely recommended for patients with good PS. Trials, mostly undertaken in the 1980s, comparing two drug regimens with three or more drug combinations showed a similar survival, although toxicity was greater with more than two drug regimens. A more recent trial reported a significant survival improvement for PE with cyclophosphamide and epidoxorubicin versus PE alone in ES patients, with no detriment in quality of life for the four-drug regimen but with a 9% toxic death rate in patients with PS 2 [11]. Multiple trials have shown that maintenance CT is not effective in improving survival, and now four to six cycles of CT is considered as optimal [3, 12, 13].

Treatment of ES with impaired PS: the poorer prognostic subgroup

Despite a general view of earlier trials, survival with PE either alone or alternating with CAV was not significantly better than CAV alone for ES patients after adjusting for prognostic factors [14–16]. However, meta-analysis of 19 trials of both LS and ES described a 4% survival benefit at 1 year if cisplatin was used [17]. Recently, a large Norwegian trial found no survival or quality of life difference between PE
and a cyclophosphamide–epirubicin–vincristine (CEV) combination in ES patients [18].

Single-agent oral etoposide, initially thought to be a good option for poorer prognosis patients, was inferior in terms of survival and was associated with more toxicity than either CAV or EV (etoposide, vincristine) or an alternating PE/CAV regimen [19, 20]. Carboplatin tends to be used as an alternative to cisplatin in poorer prognosis, higher risk patients, to avoid the higher toxicity associated with cisplatin. There is no survival difference between the two platinums, but carboplatin has a better toxicity profile [21, 22]. Indeed, single-agent carboplatin gave similar survival and symptomatic benefit with less hospitalisation when compared with the CAV regimen in a particularly poor prognosis group of patients [23]. Other conceptual approaches for infirm patients have included reduced cisplatin doses or just two courses of full dose CAV/PE [24, 25]. For newer agents, the Japan Clinical Oncology Group reported a survival benefit for the new combination irinotecan–cisplatin over PE [26]. The trial was stopped early and confirmatory trials are underway.

Given these studies, intravenous combination CT is considered to be the treatment of choice even in less fit SCLC patients. In this group of patients, PE may be appropriate but in clinical practice CbE is often used to avoid the fluid load diuresis, neurotoxicity and nephrotoxicity associated with cisplatin. More trial data are required in poorer prognosis patients to assist treatment decisions.

### Treatment of LS, good PS: the better prognostic subgroup

Standard CT includes a variety of platinum-containing regimens e.g. PE and ICE±V. The popularity of the doxorubicin-containing regimens CAV or CDE has waned over the past few years due to the use of thoracic radiotherapy concurrently with CT, which prohibits anthracycline-based CT given its marked radio-sensitisation; meta-analyses reporting better survival with PE regimens; and the Norwegian trial demonstrating survival benefit for PE over CEV in LS patients [12, 17, 18, 27]. In another large trial of better prognosis patients, ICE with mid-cycle vincristine demonstrated superior survival over standard CT, which included CDE and in some cases PE [28]. Surgical resection following CT has not improved survival. For the rare patient with a T1N0 peripheral SCLC nodule that is resected, it seems logical to give adjuvant CT.

### Combined modality treatment

#### Thoracic radiotherapy

Of major interest recently has been the incorporation of thoracic radiotherapy (TRT) into CT regimens. Meta-analysis revealed that TRT improved survival by 5% at 3 years, but there appeared to be no benefit for patients >65 years old or between early and concurrent TRT [29]. Earlier TRT given on course one or two of CT is thought by some to be better than later TRT, but only one (Canadian) trial reported this to be statistically superior [30]. Several other randomised, fully published trials have addressed the timing issue [31, 32] (Tables 1 and 2). Recently, a British group repeated the identical design of the Canadian trial, and no survival difference was found between concurrent TRT with CT during course two compared with during course six [33].

A related question is whether concurrent CT and TRT are superior to treatment given sequentially. Interpretation of available randomised trials is difficult because the question has been mixed with the issue of early versus later TRT and different TRT fractionation regimens. A Japanese study compared concurrent TRT given during course one versus sequential TRT given after course four, both with twice daily fractionation with a trend towards benefit for the earlier concurrent treatment [34]. Whether twice daily fractionation is better than once daily routine fractionation is somewhat unclear, although toxicity is increased (Table 2). The 2-year survival difference was significantly different in favour of twice daily early TRT (47% versus 41%) compared with conventional fractions starting at CT cycle one [35]. However, in another study, when TRT was given during course four either as a split course twice daily fractionation or as once daily fractionation, long-term results revealed no survival difference [36].

A recent systematic review of abstracted data described a 5% 2-year survival increase ($P=0.03$) but not significant at 3 years with early (<9 weeks from start of CT, before the third CT cycle) compared with later TRT. Subset analyses reported a greater survival benefit with platinum-based CT and twice daily TRT at both 2 and 3 years [31]. Survival at 5 years was not analysed because of a lack of data. However, the review did not include the most recent UK and USA trial results [33, 36]. When the British trial results were taken into account (in the Discussion Section) the 3-year survival improvement with early TRT and platinum-based CT became less pronounced ($P=0.07$) [31].

#### Prophylactic cranial irradiation

Meta-analysis of the impact of prophylactic cranial irradiation (PCI) described a 5% 3-year survival improvement together with reduction in incidence of brain metastases from 59% to 33% [37]. Importantly, when the cognitive testing was prospectively examined in the two largest trials, no further detriment after PCI was observed [38, 39]. The effect of PCI in patients with less than complete response to CT is unclear. Further trials of PCI are examining radiotherapy dosing and the value in ES patients with a good response to CT.

#### Dose intensification

There is a need to develop better CT regimens given the systemic nature of SCLC. A variety of strategies have been employed, e.g. maintenance treatment alternating different CT regimens (i.e. PE/CAV, etc.), but these have not been
successful [3, 12, 13]. However, if dose intensity in good prognosis patients is increased (accelerated CT with shortened cycle intervals) and dose reduction is avoided, there has been improvement in survival over standard treatment in several randomised trials [40, 41]. When the CDE regimen was used, a statistically significant small increase in median survival was found in the Medical Research Council (MRC) study with accelerated CT every 2 weeks with granulocyte colony-stimulating factor (G-CSF) compared with standard 3-week interval [42]. However, in the recent European Organisation for Research and Treatment of Cancer study, which had a more complicated factorial design and other differences from the MRC study, no significant difference was observed [43]. Much more substantial dose intensification (DI) is now

### Table 1. Timing and sequencing of thoracic radiotherapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Publication year</th>
<th>Number</th>
<th>Timing of thoracic, CT</th>
<th>PCI</th>
<th>2-year survival (%)</th>
<th>MS (months)</th>
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<tbody>
<tr>
<td>Perry, CALGB</td>
<td>1998</td>
<td>270</td>
<td>Day 1 (C)</td>
<td>Yes</td>
<td>24</td>
<td>13.0</td>
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<td></td>
<td></td>
<td>Day 64 (C)</td>
<td>Yes</td>
<td>32</td>
<td>14.5</td>
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<tr>
<td>Murray, NCIC</td>
<td>1993</td>
<td>308</td>
<td>Day 22 (C)</td>
<td>Yes</td>
<td>40</td>
<td>21.2</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Day 106 (C)</td>
<td>Yes</td>
<td>34</td>
<td>16.0</td>
</tr>
<tr>
<td>Work, Aarhus</td>
<td>1997</td>
<td>199</td>
<td>Day 1 (A)</td>
<td>Yes</td>
<td>20</td>
<td>10.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Day 120 (A)</td>
<td>Yes</td>
<td>19</td>
<td>12.0</td>
</tr>
<tr>
<td>Gregor, EORTC</td>
<td>1997</td>
<td>334</td>
<td>Day 43 (A)</td>
<td>Not mandatory</td>
<td>26</td>
<td>14.0</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Day 99 (S)</td>
<td></td>
<td>23</td>
<td>15.0</td>
</tr>
<tr>
<td>Jeremic, Yugoslav</td>
<td>1997</td>
<td>103</td>
<td>Day 1 (C)</td>
<td>Yes</td>
<td>71</td>
<td>34</td>
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<td></td>
<td></td>
<td></td>
<td>Day 43 (C)</td>
<td>Yes</td>
<td>53</td>
<td>26</td>
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<tr>
<td>Lebeau, French</td>
<td>1993</td>
<td>156</td>
<td>Day 30 (C)</td>
<td>Yes</td>
<td>13</td>
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<td>Day 36 (A)</td>
<td>Yes</td>
<td>17</td>
<td>14.0</td>
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<tr>
<td>Takada, JCOG</td>
<td>2002</td>
<td>228</td>
<td>Day 2 (C)</td>
<td>If CR or near CR</td>
<td>54</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After cycle 4 (S)</td>
<td></td>
<td>35</td>
<td>19.7</td>
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<tr>
<td>James, UK</td>
<td>2003</td>
<td>325</td>
<td>Day 22 (C)</td>
<td>Yes</td>
<td>16 (3 yrs)</td>
<td>13.5</td>
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<td>Day 106 (C)</td>
<td>Yes</td>
<td>20 (3 yrs)</td>
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<td>Skarlos, Hellenic</td>
<td>2001</td>
<td>81</td>
<td>Day 1 (C)</td>
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<td>36</td>
<td>17.5</td>
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<td></td>
<td></td>
<td>Day 64 (C)</td>
<td></td>
<td>29</td>
<td>17.0</td>
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</tbody>
</table>

Modified from references [31–33].
CT, chemotherapy; PCI, prophylactic cranial irradiation; MS, median survival; CALGB, Cancer and Leukemia Group B; NCIC, National Cancer Institute of Canada; EORTC, European Organisation for Research and Treatment of Cancer; JCOG, Japanese Clinical Oncology Group; CR, complete response; C, concurrent; A, alternating; S, sequential.

### Table 2. Hyperfractionated thoracic radiotherapy phase III, randomised controlled trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number</th>
<th>CT</th>
<th>Radiotherapy (TD, dose per fraction, timing)</th>
<th>5-year survival (%)</th>
<th>Grade 3–4 oesophagitis (%)</th>
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</thead>
<tbody>
<tr>
<td>Jeremic, Yugoslav</td>
<td>103</td>
<td>CbE</td>
<td>54 Gy, 1.5 Gy bd, weeks 1–4</td>
<td>30.0</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>54 Gy, 1.5 Gy bd, weeks 6–9</td>
<td>15.0</td>
<td>13</td>
</tr>
<tr>
<td>Takada, JCOG</td>
<td>228</td>
<td>PE</td>
<td>45 Gy, 1.5 Gy bd, weeks 1–3</td>
<td>23.7</td>
<td>9</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>45 Gy, 1.5 Gy bd, after week 10</td>
<td>18.3</td>
<td>4</td>
</tr>
<tr>
<td>Turrisi, USA</td>
<td>417</td>
<td>PE</td>
<td>45 Gy, 1.5 Gy bd, weeks 1–3</td>
<td>26.0</td>
<td>32</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>45 Gy, 1.8 Gy od, weeks 1–5</td>
<td>16.0</td>
<td>16</td>
</tr>
<tr>
<td>Schild, NCCTG</td>
<td>262</td>
<td>PE</td>
<td>48 Gy, 1.5 Gy bd, weeks 13–14, then 17–18</td>
<td>22.0</td>
<td>12.3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>50.4 Gy, 1.8 Gy od, weeks 13–18</td>
<td>21.0</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Modified from references [31, 32, 34–36].
CT, chemotherapy; TD, total dose; JCOG, Japanese Clinical Oncology Group; NCCTG, North Central Cancer Treatment Group; CbE, carboplatin–etoposide; PE, cisplatin–etoposide; bd, twice daily; od, once daily.
possible using peripheral blood stem cells harvested after G-CSF priming. The stem cells can be conveniently re-infused. Disappointingly, the follow-up phase III trial did not demonstrate a survival benefit for DI over standard CT [44]. However, a smaller German trial did indicate a survival benefit [45].

New agents

Treatment for patients with SCLC and a good PS might be improved by the use of novel agents. Recently, a German trial compared a paclitaxel, carboplatin and etoposide regimen against a standard regimen of carboplatin, etoposide and vincristine, and reported a statistically significant survival benefit (12.7 versus 11.7 months) for the paclitaxel regimen. In LS but not in ES patients, a statistically significant survival gain remained [46]. However, this result has not been replicated in two other studies of paclitaxel added to a standard PE regimen [12].

Salvage CT and new agents

Survival following relapse from first-line CT is generally poor, with a median of ~4 months. Patients can be separated into sensitive and resistant subgroups to subsequent CT based on response to first-line CT and the progression-free interval. The sensitive subgroup includes those patients who have previously responded and who have had a relapse-free interval of at least 3 months. Re-induction with the same first-line CT is an option. However, this may not be possible owing to reduced tolerance or increased toxicity. The other non-sensitive resistant patients are candidates for new approaches [47]. Radiotherapy and other palliative treatments should also be considered. New drugs have been examined generally in patients with ES, and in patients who have progressed. Topotecan has shown a benefit in terms of symptom control, with equivalent survival and response rate to a CAV regimen. An oral preparation is undergoing evaluation [48]. Approaches using BEC2/BCG vaccination and Marinomastate have been ineffective, but other interesting drugs include taxanes, gemcitabine, vinorelbine, novel platinum and a plethora of new ‘targeted’ therapies [49].

Conclusions

There has perhaps been a loss of focus on SCLC given the advent of more successful treatment in non-SCLC. There remains a need to develop better treatments, particularly for the majority of patients with ES disease and impaired PS. It is important to emphasise, however, that SCLC is a very chemosensitive tumour, and the newer methods of integrating chemoradiotherapy together with new drug development hold considerable promise for the future.

References


