Review

The combination of etoposide and cisplatin in non-small-cell lung cancer (NSCLC)

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Summary

The role of chemotherapy in the treatment of advanced non-small-cell lung cancer (NSCLC) has been a subject of debate for many years. Only recently, cisplatin-based combination chemotherapy has been demonstrated to yield a small but definite survival benefit and to improve symptoms, performance status and quality of life in a substantial proportion of advanced NSCLC patients. The cisplatin-etoposide (PE) regimen was developed in the early 1980s and has been one of the standard chemotherapy programs most extensively used in the clinical practice until a few years ago. More recently, several randomized trials have compared the efficacy of new cisplatin-containing combination chemotherapies including Paclitaxel or Gemcitabine with that of PE or PE-like regimens. Preliminary results are encouraging, indicating a small benefit in favor of the last generation of regimens which might therefore replace PE as 'gold standards' in the treatment of advanced NSCLC. However, the costs of these last generation regimens is higher and the entity of the benefit small. Therefore, PE chemotherapy can still be an option in selected situations.

Key words: advanced disease, chemotherapy, cisplatin, etoposide, non-small-cell lung cancer

Introduction

The combination of cisplatin and etoposide belongs to the history of NSCLC chemotherapy. The role of chemotherapy in the treatment of advanced NSCLC has been a subject of debate for many years. During those years, the cisplatin-etoposide regimen was among the most frequently used in clinical practice. While the role of chemotherapy in this disease was becoming more clear, thanks to a recent meta-analyses indicating that cisplatin-based chemotherapy improves survival in NSCLC patients of all stages, and to a number of non-randomized studies showing a significant effect of chemotherapy in symptom control, new, and probably more effective, regimens have been developed.

This paper will review the results of cisplatin-etoposide combination chemotherapy and will discuss the present role of this regimen in the treatment of advanced NSCLC.

The development of cisplatin-etoposide combination chemotherapy

Before the 1980s, few agents had shown antitumor activity in NSCLC with response rates usually below 10%. When these agents were combined in 2–3-drug combination chemotherapy regimens, response rate was only slightly improved and impact on survival still uncertain. Chemotherapy regimens of this period are referred as ‘first-generation’ regimens.

In the 1980s, new agents with activity in the treatment of NSCLC included cisplatin, mitomycin-C, ifosfamide, vindesine, vinblastine, carboplatin and etoposide. Objective response rate with these drugs was usually in the range of 10%-20% with 10%-20% one-year survival rate. Several two-drug or three-drug regimens have undergone clinical trials with a reported response rate of 20%-40%. These ‘second generation’ regimens, including the combination of cisplatin and etoposide, are those which have been used to prove the role of chemotherapy in the treatment of NSCLC. Second-generation cisplatin-containing regimens have been proved to produce a small survival improvement in patients submitted to radical surgery as compared to no adjuvant treatment, in patients with locally advanced inoperable disease when added to thoracic radiotherapy as compared to radiotherapy alone and, finally, in patients with metastatic disease when compared to best supportive care only [1]. In addition, a number of uncontrolled trials have indicated the ability of cisplatin-containing chemotherapy to yield a symptomatic improvement in nearly half of the patients [2].

Cisplatin-etoposide combination chemotherapy was developed in the early 1980s, based on experimental data demonstrating antitumor synergism of these two agents in animals and laboratory models [3]. Early phase II studies carried out in the 1980s with this combination chemotherapy reported response rates ranging from 19%-52% [4–8] (Table 1).
was evaluated in a phase II study [13] with encouraging results in terms of response rate but hematological toxicity was dose-limiting. Similar results were obtained by Veronesi et al. using a more protracted oral etoposide. The long-term daily administration of oral etoposide in combination with cisplatin was evaluated in a phase II study [13] with encouraging results in terms of response rate but hematological toxicity was dose-limiting. Similar results were obtained by Planting et al. [14] using a more protracted oral etoposide schedule in combination with weekly cisplatin. This type of regimen has also been used in combination with concurrent chest irradiation in patients with locally advanced inoperable NSCLC [15].

**Cisplatin-etoposide-based triple-drug regimens**

To improve the results achieved with PE, the next step was to add a third active agent to this regimen. Cisplatin plus etoposide has been evaluated in combination with vindesine [16], vincristine [17], bleomycin [18] and ifosfamide [19] with promising results as reported in Table 4. However, two randomized trials failed to demonstrate any superior activity with the addition of vindesine [20] or ifosfamide [21] to cisplatin-etoposide combination chemotherapy.

**Cisplatin-etoposide vs. ‘first-generation’ regimens not containing cisplatin**

Table 2 reports the results of some of the studies which compared CAMP, or other ‘first-generation’ regimens, to PE. Response rate was in general higher for PE while differences in terms of survival were not always statistically significant. The discrepancy between the different studies regarding overall response and survival with PE can be explained in part by differences in selection criteria (i.e., percentage of patients with stage III vs. stage IV), in the schedule of PE administration, and in the occasional use of radiotherapy in responders [22–25].

**Cisplatin-etoposide combination vs. single-agent chemotherapy**

To verify whether cisplatin added to etoposide really offered an advantage over etoposide alone, the Italian Lung Cancer Task Force conducted a randomized study (PE vs. E alone) demonstrating that combination chemotherapy increased tumor response from 7%–25.8% \( (P < 0.005) \) with a two-month prolongation in median survival which, however, did not reach statistical significance [26].

In the same period, two studies comparing cisplatin plus etoposide with single-agent cisplatin led to different conclusions (Table 3). Crino et al. compared [21] to cisplatin-etoposide combination chemotherapy. Cisplatin-etoposide-based triple-drug regimens

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### Table 1. Summary of early clinical studies using cisplatin and etoposide in NSCLC.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Cisplatin (mg/m²)</th>
<th>Etoposide (mg/m²)</th>
<th>Number of patients</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldhirsch, 1981</td>
<td>100</td>
<td>80 x 3</td>
<td>18</td>
<td>39</td>
</tr>
<tr>
<td>Longevial, 1982</td>
<td>60</td>
<td>120 x 3</td>
<td>94</td>
<td>37</td>
</tr>
<tr>
<td>Veronesi, 1983</td>
<td>100</td>
<td>75 x 5</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Mitrou, 1984</td>
<td>90</td>
<td>100 x 3</td>
<td>46</td>
<td>32</td>
</tr>
<tr>
<td>Ardizzoni, 1986</td>
<td>60 x 2</td>
<td>120 x 3</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

**Cisplatin-etoposide dose and schedule**

Etoposide, in combination with cisplatin, has been most commonly given i.v. over 30–60' at doses from 80–120 mg/m² on days 1–3 or 1, 3, 5 or 1–5. Cisplatin has been usually administered i.v. on day 1 at doses ranging from 60 mg/m² to 120 mg/m². Klastersky et al. compared high (120 mg/m²) with standard dose (60 mg/m²) of cisplatin in combination with etoposide, reporting 29% and 25% objective response respectively \( (P = 0.49) \). The median overall survival was 28 weeks with high dose and 33 weeks with standard dose \( (P = 0.138) \). Toxicity was tolerable in both arms [9]. These results, indicating the lack of a dose-response relationship are in contrast with those originally reported by Gralla et al. [10] suggesting superiority of high-dose cisplatin.

A number of attempts have been made to modify the schedule of administration of PE. Laboratory studies suggested that therapeutic synergism between cisplatin and etoposide could be related to factors of drug concentration, time of exposure, and sequencing. In addition, activity of etoposide is clearly schedule-dependent. A phase I–II study tested etoposide given by 72 hours infusion in conjunction with sequential bolus or infusional cisplatin reporting a promising therapeutic activity for infusional etoposide followed by cisplatin [11]. Successively, the North Central Cancer Treatment Group, in a phase III randomized trial [12] compared an outpatient bolus regimen of PE with a sequential infusion over 72 hours of these same two drugs in stage IV NSCLC. A major response was observed in 37% vs. 30% of patients with a median survival of 148 and 157 days respectively \( (P = 0.71) \). The conclusions were that the infusion regimen, which is associated with a higher toxicity, did not produce any advantage in response rate and survival as compared with bolus treatment.

The good bioavailability of oral etoposide, along with the clear relationship between drug exposure and antitumor activity in preclinical models, prompted a series of studies assessing the combination of cisplatin and protracted oral etoposide. The long-term daily administration of oral etoposide in combination with cisplatin was evaluated in a phase II study [13] with encouraging results in terms of response rate but hematological toxicity was dose-limiting. Similar results were obtained by Planting et al. [14] using a more protracted oral etoposide schedule in combination with weekly cisplatin. This type of regimen has also been used in combination with concurrent chest irradiation in patients with locally advanced inoperable NSCLC [15].

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higher for both MIC (40%) and MVP (36%) than for PE (23%). Median survival was 42 weeks for MVP, 36 for PE. Response rate were statistically randomised trials did not report any advantages with MIC and 27 for PE (P < 0.04). On the contrary, other randomized trials did not report any advantages with MVP. A large randomized three-arm trial [29] compared PE, chosen as standard treatment, with two of the most active three-drug regimens, MVP and MIC.

Table 2. Randomized study comparing PE with 'first-generation' regimens.

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>Number of patients</th>
<th>OR (%)</th>
<th>S (weeks)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joss</td>
<td>DOXO-MMC</td>
<td>37</td>
<td>11</td>
<td>30</td>
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</tr>
<tr>
<td></td>
<td>PE</td>
<td>40</td>
<td>23</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAMP</td>
<td>115</td>
<td>17</td>
<td>25.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MVP</td>
<td>121</td>
<td>31</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>124</td>
<td>20</td>
<td>26.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VDA-P</td>
<td>126</td>
<td>25</td>
<td>26.0</td>
<td></td>
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<tr>
<td></td>
<td>Veronesi</td>
<td>CAMP</td>
<td>62</td>
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<tr>
<td></td>
<td>PE</td>
<td>71</td>
<td>38.2</td>
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<tr>
<td></td>
<td>Paccagnella</td>
<td>VDA-P</td>
<td>31</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>33</td>
<td>36</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DOXO-CTX</td>
<td>30</td>
<td>10</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>


* Statistically significant difference in response rate.

* No significant difference in response for patients treated with Taxol-DDP-G-CSF.

Table 3. Randomized trials comparing cisplatin-etoposide with single-agent cisplatin or etoposide.

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>Number of patients</th>
<th>OR (%)</th>
<th>S (weeks)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klastersky</td>
<td>DDP</td>
<td>74</td>
<td>19</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>72</td>
<td>26</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Crinò</td>
<td>DDP</td>
<td>24</td>
<td>4</td>
<td>18</td>
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</tr>
<tr>
<td></td>
<td>PE</td>
<td>69</td>
<td>30</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEM</td>
<td>57</td>
<td>26</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Rosso</td>
<td>PE</td>
<td>103</td>
<td>25.8</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>113</td>
<td>7</td>
<td>25.7</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PEM – cisplatin-etoposide-mitomycin C.

ried out by the Lung Cancer Working Party there was only a trend toward a better response rate in patients treated with cisplatin etoposide as compared to those treated with single-agent cisplatin [20].

### Cisplatin-etoposide vs. other cisplatin-containing 'second-generation' regimens

Cisplatin-etoposide has been compared with other second-generation cisplatin-containing regimens. In general, no difference has been found with other two-drug regimens, while results of studies comparing PE with three-drug regimens were contradictory. A large randomized three-arm trial [29] compared PE, chosen as standard treatment, with two of the most active three-drug regimens, MVP and MIC. Response rate were statistically higher for both MIC (40%) and MVP (36%) than for PE (23%). Median survival was 42 weeks for MVP, 36 for MIC and 27 for PE (P < 0.04). On the contrary, other randomized trials did not report any advantages with PE, MVP and MIC. Response rate were statistically randomised trials did not report any advantages with MIC and 27 for PE (P < 0.04). On the contrary, other randomized trials did not report any advantages with MVP. A large randomized three-arm trial [29] compared PE, chosen as standard treatment, with two of the most active three-drug regimens, MVP and MIC. Response rate were statistically higher for both MIC (40%) and MVP (36%) than for PE (23%). Median survival was 42 weeks for MVP, 36 for MIC and 27 for PE (P < 0.04). On the contrary, other randomized trials did not report any advantages with PE, MVP and MIC.

### Effect of additional chemotherapeutic agents on efficacy of cisplatin-etoposide combination chemotherapy

Table 4. Effect of additional chemotherapeutic agents on efficacy of cisplatin-etoposide combination chemotherapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>Number of patients</th>
<th>OR (%)</th>
<th>S (weeks)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klastersky</td>
<td>DDP-VP16-VDS</td>
<td>62</td>
<td>40</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Bertrand</td>
<td>DDP-VP16-VCR</td>
<td>22</td>
<td>27</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Osoba</td>
<td>DDP-VP16-BLM</td>
<td>48</td>
<td>44</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Ardizzoni</td>
<td>IFO-DDP-VP16</td>
<td>42</td>
<td>26.2</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: GEM – gemcitabine.

* Not statistically significant.

* No significant difference in response for patients treated with Taxol–DDP vs. Taxol–DDP–G-CSF.

three-drug cisplatin-based combination chemotherapy [20, 23].

### Cisplatin-etoposide vs. ‘third generation’ drugs and regimens

At the beginning of the 1990s, a number of new active drugs have become available for the treatment of NSCLC. Among these, paclitaxel and gemcitabine have been the most extensively studied with average response rates over 20%. When combined with cisplatin, response rates raised to 40%–50%. Recently, several randomized trials have evaluated the role of these new drugs and regimens in comparison with PE, used as control regimen (Table 5). Single-agent gemcitabine was compared with PE in two phase II randomized trials. The results in terms of overall response reported by Manegold et al. [30] were not statistically significant. In fact, objective response rate was 18.2% with cisplatin and etoposide regimen compared to 15.3% for gemcitabine as a single-agent. Perng et al. [31] confirmed that gemcitabine alone has comparable efficacy to cisplatin plus etoposide regimen with lower toxicity.

Based on preclinical results indicating synergism between cisplatin and gemcitabine, this combination became one of the investigational arms in a randomized study conducted by the Spanish Lung Cancer Group. In a preliminary report, the overall response rate achieved with this new combination was better than that obtained
in the PE arm (49% vs. 28%). Thrombocytopenia was the major toxicity observed with gemcitabine plus cisplatin. Final analysis of this trial is still ongoing [32]. Another new combination chemotherapy program which is undergoing extensive evaluation in NSCLC is paclitaxel plus cisplatin. A randomized study has been conducted by the ECOG to compare the combination of paclitaxel and cisplatin against a standard regimen of cisplatin and etoposide. In this three-arm trial, 571 untreated patients were eligible to receive PE versus either high-dose (250 mg/m² with G-CSF) or low-dose (135 mg/m²²) paclitaxel in combination with cisplatin at the dose of 75 mg/m². Both paclitaxel regimens were associated with a significantly higher response rate, and preliminary survival data suggest a trend toward a longer survival in patients treated with this new combination chemotherapy [33].

Conclusions

Does cisplatin–etoposide combination chemotherapy regimen still have any place in the standard treatment of NSCLC? In most instances, it is likely that this combination chemotherapy will be replaced by third-generation regimens. However, there are three situations in which cisplatin–etoposide could still play a role.

First, there are lung cancer patients in which a clear distinction between small-cell and non-small-cell cannot be made, either because of difficulties in the histological subtyping, or because of difficulties in obtaining adequate tumor samples for histological diagnosis. In this not so rare condition, cisplatin-etoposide can represent a valuable option in the clinical practice, being standard patients with stage IV NSCLC.

Second, cost issues [34] with third-generation regimens in NSCLC are of concern (Table 6). One may argue whether a one-month increase in survival and/or a 15% increase in response rate for an incurable disease justifies the increase in costs due to the use of third-generation drugs as opposed to second-generation ones. In situations of hospital budget restrictions, second-generation cisplatin-containing chemotherapy, such as cisplatin–etoposide, may still represent a reasonable choice for patients with stage IV NSCLC.

Finally, cisplatin–etoposide combination chemotherapy has been extensively used in combination with concomitant chest irradiation with positive results and acceptable toxicity in both SCLC and NSCLC. Particularly, the Radiation Therapy Oncology Group in the US has reported 35% two-year survival and 19 months median survival in patients with stage II–IIIB inoperable NSCLC treated with cisplatin plus continuous oral etoposide and concomitant bifractionated radiotherapy [15]. This regimen is presently being compared to other sequential or concomitant chemoradiotherapy programs in a phase III RTOG study. Should this study demonstrate a superiority of this regimen or equivalence with reduced toxicity, cisplatin–etoposide combination chemotherapy could still be considered ‘alive and well’ in the treatment of NSCLC.

References


Table 6. Additional costs of newer chemotherapeutic agents compared to cisplatin–etoposide (Canadian Dollars per year life saved).

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Additional cost per year life saved (CDN $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVB–DDP</td>
<td>8,566</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>12,116</td>
</tr>
<tr>
<td>GEM</td>
<td>10,963</td>
</tr>
</tbody>
</table>

Abbreviations: NVB–DDP = navelbine–cisplatin; GEM = gemcitabine. Adapted from Earle et al. [34].


