Anthracyclines in non-small-cell lung cancer: Do they have a therapeutic role?

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See page 22 for a list of participating institutions and investigators to phase III trial HD-EPI + CP vs. VNR + CP

Summary

Background: Owing to its low level of activity together with its potential cardiotoxicity, doxorubicin (DXR) has been considered as having a marginal role in the treatment of NSCLC. Its analogue, epirubicin (EPI), has also shown a poor antitumor activity in the treatment of NSCLC when used at 'standard' doses (= 90 mg/m²). On the contrary, high-dose epirubicin (HD-EPI) (> 90 mg/m²) has demonstrated antitumor activity as a single agent in the treatment of advanced NSCLC in six small phase II studies (mean 25%, range 17%-36%).

Results: A series of consecutive studies on the activity of HD-EPI alone or in combination regimens were carried out at the Division of Medical Oncology of S. Orsola-Malpighi Hospital. After activity was confirmed in advanced disease with doses between 120 and 165 mg/m² (PR in 6 of 24 = 25%), a phase II study was carried out on the combination of HD-EPI 120 mg/m² + cisplatinum (CP) 60 mg/m² in stage IIIB-IV NSCLC. PR was achieved in 54% of 35 patients with a median survival of nine months. A subsequent multicenter phase III trial compared HD-EPI and vinorelbine (VNR), both combined with CP. Two hundred twenty-eight patients with locally advanced or metastatic NSCLC were randomized to receive either EPI 120 mg/m² plus CP 60 mg/m² on day 1 or VNR 25 mg/m² on day 1 and 8 plus CP 60 mg/m² on day 1. Both treatments were recycled every 21 days. Eligible patients were 212 and 210 patients evaluable for objective response (100 on HD-EPI and 110 on VNR), respectively. The CR + PR rate was 32% vs. 26% (P = NS) for a median duration of nine and eight months, respectively. Median survival was 10 and 9.5 months, respectively. Grade III—IV leucopenia occurred in 38% and 21% on HD-EPI and VNR, respectively (P = 0.01), thrombocytopenia in 6% and 0% (P = 0.02), anemia in 8% and 7% (NS). Non-hematological toxicity was moderate and the only difference between the treatments was alopecia (88% vs. 33% on HD-EPI and VNR, respectively). Supraventricular arrhythmia occurred in three patients on HD-EPI; a > 15% LVEF decrease by MUGA scan was observed in 22.5% and 14% patients on HD-EPI and VNR, respectively (NS). No congestive heart failure was observed.

Conclusions: EPI can be safely administered at a dose of 120-135 mg/m² in non-pretreated patients showing a significant antitumor activity in NSCLC. If the cumulative dose of 800-900 mg/m² is not exceeded, clinical manifestations of cardiotoxicity are very rare. However, grade 3-4 myelotoxicity and alopecia are very common and can limit the use of this drug in the palliative treatment of this disease. Interesting results are observed in an ongoing pilot study that employed HD-EPI + CP + VNR + G-CSF in the induction therapy of locally advanced NSCLC.

Key words: high-dose epirubicin, non-small-cell lung cancer

Introduction

At the end of the 1980s, drugs such as cisplatin, mitomycin C, ifosfamide, vindesine and vinblastine demonstrating antitumor activity ≥ 15%, were considered the agents of reference in chemotherapy for NSCLC, although the role of chemotherapy in the treatment of this disease was still under discussion. In recent years, new interest has been aroused in NSCLC chemotherapy following the availability of new active cytotoxic agents like Taxanes, Camptotecins and Gemcitabine. On the other hand, comparatively little attention has been paid to the use of anthracyclines. In a review of trials concerning the activity of cytotoxic drugs in NSCLC, doxorubicin (DXR) induced an objective remission in 12% out of a total of 296 patients [1]. This low level of activity together with its potential cardiotoxicity contributes to determining a marginal role, if any, in the treatment of NSCLC.

HD-EPI in advanced NSCLC

Epirubicin (EPI) is an analogue of DXR which has demonstrated a similar antitumor spectrum of activity and less cardiotoxicity. EPI, like its parent drug DXR, has shown a poor antitumor activity in the treatment of NSCLC when used at 'standard' doses (≤ 90 mg/m², Table 1).

At the end of 1980, a re-evaluation of the dose to be used as first-line antitumor treatment was made. Initial phase I EPI trials were carried out on patients with important conditions limiting the tolerability of the drug such as previous myelotoxic treatments, and diffuse liver...
Table 1. Epirubicin in advanced NSCLC activity of standard doses (≤90 mg/m²).

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Dose (mg/m²) every 21–28 days</th>
<th>Number of patients</th>
<th>Response (CR + PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalman [2]</td>
<td>65–85</td>
<td>34</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Martoni [3]</td>
<td>90</td>
<td>17</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Joss [4]</td>
<td>90</td>
<td>75</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Meyers [5]</td>
<td>75</td>
<td>64</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Furuse [6]</td>
<td>60</td>
<td>33</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>223</td>
<td>12 (5%)             (95% CI: 3%–9%)</td>
</tr>
</tbody>
</table>

Table 2. Epirubicin in advanced NSCLC activity of high doses (>90 mg/m²).

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Dose (mg/m²) every 21–28 days</th>
<th>Number of patients</th>
<th>Response (CR + PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feld [9]</td>
<td>35–60 daily × 3 d</td>
<td>33</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Holdener [10]</td>
<td>120–190</td>
<td>12</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Hens [11]</td>
<td>150</td>
<td>18</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Wils [12]</td>
<td>135–150</td>
<td>24</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>Martoni [8]</td>
<td>120–165</td>
<td>24</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>Smit [13]</td>
<td>135</td>
<td>25</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>34</td>
<td>25 (25%)           (95% CI: 17%–32%)</td>
</tr>
</tbody>
</table>

metastases, together with general factors such as old age and low performance status. On these grounds, a series of new phase I studies was subsequently designed. One of these studies was carried out at our Division for patients with refractory advanced tumors not previously treated with myelosuppressive therapies and without liver metastasis, in order to define the maximum tolerated dose (MTD) [7]. EPI was administered as bolus i.v. at the initial dose of 105 mg/m² and a 15 mg/m² dose escalation step was performed according to standard phase I study methodology. Eighteen patients were admitted to the study. MTD was reached at 165 mg/m². The dose-limiting toxicities were neutropenia and a decrease in performance status. The other side-effects were nausea-vomiting (78%) and alopecia (100%). Four patients (22%) stopped the treatment because of a > 10% decrease in left ventricular ejection fraction (LVEF) by MUGA scan at rest, without clinical signs of cardiotoxicity. A partial remission (PR) was observed in two out of seven patients with unresectable NSCLC at the dose levels of 135 and 150 mg/m², respectively.

On the basis of these results we enlarged our experience in the use of high-dose EPI (HD-EPI) in NSCLC. This experience included a total of 24 patients with unresectable NSCLC (14 stage III B and 10 stage IV) who received HD-EPI as i.v. bolus at a dose ranging between 120 and 165 mg/m² every 21–28 days up to the maximum cumulative dose of 900 mg/m² [8]. Six patients (25%) achieved PR for a median duration of 7.5 months. The median dose actually administered per course was 120 mg/m² in responsive and non-responsive patients. The median survival was 10 months (range 1–16). These data suggested that HD-EPI might have a higher antitumor activity than standard doses in patients with NSCLC. These results were in agreement with those of other authors. In Table 2 the results of six small trials on HD-EPI in advanced NSCLC are summarized. Out of a total of 136 patients an objective remission was reported in 25% (17%–36%) of cases. The conclusions of all the authors were that HD EPI was an active treatment in advanced NSCLC.

HD-EPI in combination chemotherapy: Phase II studies

Subsequent to these observations our next step was to conduct a phase II study on the combination of HD-EPI and cisplatin (CP) [14]. Thirty-seven patients with unresectable NSCLC (13 stage III, and 24 stage IV) received EPI as an i.v. bolus at the dose of 120 mg/m² + CP at the dose of 60 mg/m² every 28 days up to the maximum cumulative dose of 840 mg/m² of EPI. Out of 35 evaluable patients 19 (54%) achieved PR for a median duration of 10 months. The majority of responsive patients also experienced an improvement in performance status, related-disease symptoms and body weight. Grade 3–4 leucopenia occurred in 42% of the patients. In five patients (14%) there was a > 10% reduction in the LVEF calculated by MUGA scan. None of these patients suffered from cardiac symptoms. The median survival was 9 months (range 2–26). This study showed that the inclusion of HD-EPI in a combination regimen had contributed to obtaining a high remission rate in advanced NSCLC.

Another study on HD-EPI (135 mg/m²) combined with etoposide 60 mg/m²/day for 3 days in 25 unresectable NSCLC patients was carried out in the Netherlands. Objective remission was observed in 9 (36%) with a median survival of 31 weeks. In this study the addition of low-dose etoposide, according to the authors, did not offer any advantages over HD-EPI alone [15].

HD-EPI in phase III study

Since no randomized study comparing HD-EPI as a single agent or in combination with other cytotoxic drugs versus other active combination regimens has been undertaken in patients with NSCLC, we decided to compare the regimen HD-EPI + CP with a standard regimen for the treatment of this disease.

The vinca derivative vinorelbine (VNR) had been shown to be active in the treatment of NSCLC and less neurotoxic than other vinca alkaloids [16]. In a multi-center randomized study the combination of VNR + CP had been superior to the combination of vindesine + CP both in terms of objective response and survival [17]. Hence, the VNR + CP combination was acknowledged...
in Europe as being one of the standard regimens in the treatment of NSCLC.

A multicenter study (see participating institutions at the end of the text) was undertaken with the aim of comparing efficacy (antitumor response, time-to-progression, survival and toxicity) of HD-EPI or VNR both combined with the same dose of CP in the treatment of advanced NSCLC. Patient eligibility criteria for inclusion in the study were histological or cytological diagnosis of unresectable measurable NSCLC, age ≤ 72 years, performance status (PS) ≥ 70% according to Karnofsky, no previous chemotherapy or radiotherapy, absence of symptomatic brain metastases, absence of liver metastases with diameter > 2 cm, LVEF by MUGA scan or echography, adequate marrow, hepatic and renal functions.

Patients were randomized to receive either HD-EPI + CP or VNR + CP. EPI was administered at the dose of 120 mg/m² by i.v. bolus and CP at the dose of 60 mg/m² in one hour by i.v. on day 1. VNR was administered at the dose of 25 mg/m² by i.v. bolus on day 1 and 8 and CP as above on day 1. Both regimens were recycled every 21 days. The treatment was continued until progression or a maximum of 12 cycles (EPI was nonetheless stopped at the cumulative dose of 800–840 mg/m²).

The number of patients to be enrolled in the study was calculated on the basis of the expected overall tumor response. An overall objective response of 25% for the reference treatment (VNR + CP) was assumed, and a difference of 20% in the CR + PR rate between the reference treatment and the new treatment (HD-EPI + CP) was considered to be of clinical interest. Setting \( \alpha = 0.05 \) and power \((1-\beta) = 0.8\), one-tail level of significance, a sample size of 94 evaluable patients per treatment arm was computed.

Preliminary results of this study had been previously published [18] and here we summarize the definitive results. From August 1992 to February 1996, 228 patients were randomized to receive either HD-EPI + CP (112 patients) or VNR + CP (116 patients). Sixteen ineligible patients were excluded from the analysis. The main characteristics of the eligible patients were male/female 179/33, median age 61 (42–72), median PS 80 (70–100), epidermoid carcinoma 101, adenocarcinoma 76, other histotypes 35, stage IIIA 25, stage IIIB 85, stage IV 88, recurrence 14. The two groups were well-balanced and there was no statistically significant difference in the distribution of prognostic factors.

All eligible patients were included in the objective response analysis even if 14 patients (7 in each arm) were not evaluable. The analysis of the objective response is reported in Table 3. Complete remission (CR) was observed in one and two patients on HD-EPI and VNR, respectively. PR occurred in 32 and 27 patients on HD-EPI and VNR, respectively. The CR + PR rate was 32% (95% confidence intervals (95% CI): 24%–43%) vs. 26% (95% CI: 18%–35%). Median duration of remission was 9 (range 4–22) months and 8 (3–34+) months in HD-EPI and VNR, respectively, and the median time to progression was 6 and 5 months, respectively. Response was not related to stage and histotype.

A > 10 improvement in PS was recorded in 37% and 39% of patients. An improvement in at least one symptom such as cough, dyspnoea and pain without a worsening or the appearance of another one was recorded in 57% and 61% of symptomatic patients, respectively. No difference was statistically significant.

Myelosuppression was the most frequent side-effect. Grade 3–4 leukopenia occurred in 38% of patients on HD EPI and in 21% of patients on VNR \((P = 0.013)\). Febrile neutropenia was observed in five and three patients on HD-EPI and VNR, respectively. Grade 3–4 anemia was observed in 8% and 7%, respectively (NS) and grade 3–4 thrombocytopenia was only observed in HD-EPI (6%, \(P = 0.018\)). Grade 3 non-hematological toxicity was only represented by vomiting (8% HD-EPI and 4% VNR, NS); stomatitis, local reactions in the site of i.v. injection, fever, neurotoxicity, diarrhoea and an increase in creatinine occurred only at a grade 1–2 intensity with a low incidence and without any significant difference between the two arms. Alopecia was more frequent on HD-EPI arm (88% vs. 33%, \(P = 0.0001\)). Three patients presented atrial tachyarrhythmia during the HD-EPI treatment. A > 15% LVEF decrease was observed in 9 of 40 (22.5%) and 3 of 22 (14%) patients on HD-EPI and VNR, respectively (no statistically significant difference). No congestive heart failure was observed.

Excluding 15 patients (8 patients on HD-EPI and 7 on VNR) radically operated and 2 patients lost to follow-up, the median survival was 10 months (95% CI: 9–11 months) and 9.5 months (95% CI: 7.7–10.8 months) on HD-EPI and VNR, respectively (Table 4). Twelve-month survival was 43% and 37% on HD-EPI and VNR.

Therefore, this phase III trial shows that HD-EPI + CP and VNR + CP, in accordance with the adopted schedules, were both active combinations in advanced NSCLC, sharing a similar objective response rate, response duration, subjective response and survival. HD-EPI + CP was associated with a higher incidence of myelosuppression and alopecia, but did not show any clinically significant cardiotoxicity. In addition, from this trial HD-EPI was confirmed as being an active and

### Table 3. Phase III study HD-EPI + CP vs. VNR + CP in advanced NSCLC. Objective response (intent to treat analysis).

<table>
<thead>
<tr>
<th>Eligible patients</th>
<th>HD-EPI + CP</th>
<th>VNR + CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not evaluable</td>
<td>7 (7%)</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>PR</td>
<td>32 (31%)</td>
<td>27 (24.5%)</td>
</tr>
<tr>
<td>MR</td>
<td>14 (14%)</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>NC</td>
<td>28 (27%)</td>
<td>31 (28%)</td>
</tr>
<tr>
<td>P</td>
<td>20 (20%)</td>
<td>30 (27%)</td>
</tr>
</tbody>
</table>

\( P = NS \)

Median response duration (months) 9 8
Median time to progression (months) 6 5

...
NSCLC is, in our opinion, warranted as the initial modern palliative treatment of this disease. A larger study in the induction treatment of locally advanced NSCLC is, in our opinion, warranted as the initial modern palliative treatment of this disease. A larger study in the induction treatment of locally advanced NSCLC.

Pilot study on HD-EPI-based chemotherapy in the induction treatment for locally advanced NSCLC

As a result of the above-described phase III trial, we have designed a pilot study on the combination of HD-EPI + CP + VNR with G-CSF support in the neoadjuvant therapy of locally advanced NSCLC. The drug schedule was as follows: EPI 120 mg/m² on day 1, CP 75 mg/m² on day 1 and VNR 25 mg/m² on day 1 and 15, G-CSF 300 mg s.c. daily from day 3 to 12 with recycling every 21 days for three cycles. All patients were re-staged after the third cycle and re-evaluated for surgical resection. So far 13 patients have entered this pilot study (11 males and 2 females, median age 54, median PS 90, 11 stage IIIA/N2 and 2 stage IIIB). After three cycles 11 of 12 evaluable patients presented PR and 1 NC. Two patients were considered unresectable because of persistance of N2, one patient resulted N3 at mediastinoscopy and one patient refused the operation. Eight patients were operated on: six (50%) were resected and in two the operation was only exploratory.

Conclusions

EPI is the most studied anthracycline in the treatment of NSCLC. This drug can be safely administered at a dose of 120–135 mg/m² in non-pretreated patients showing a significant antitumor activity in NSCLC. If the cumulative dose of 800–900 mg/m² is not exceeded, clinical manifestations of cardiotoxicity are very rare. However, grade 3–4 myelotoxicity and alopecia are very common and can limit the use of this drug in the modern palliative treatment of this disease. A larger study in the induction treatment of locally advanced NSCLC is, in our opinion, warranted as the initial results in this setting seem to be promising.

*Appendix

Institutions and Investigators participating in a phase III trial of HD-EPI + CP vs. VNR + CP

Divisione di Oncologia Medica, Ospedale S. Orsola–M. Malpighi, Bologna (A. Martoni, M. Guaraldi, E. Piana, E. Strocchi, F. Pannuti); Divisione di Radioterapia Ospedale S. Orsola-Malpighi, Bologna (L. Busutti, A. Petralia); Divisione di Oncologia Medica, Fondazione Clinica del Lavoro, Pavia (G. Robustelli della Cuna, P. Preti); Divisione di Oncologia Medica, Ospedale 'Casali Sollevio della Sofferenza', S. Giovanni Rotondo (FG) (G. Lelli, G. Palomba); Divisione di Oncologia Medica, Ospedale S. Cuore, Negrar (VR) (E. Recaldin, V. Fieve); Servizio di Oncologia Medica, Ospedale S.Chiara, Trento (G. Ambrosini, O. Caffo); Cattedra di Oncologia Medica, Università di Sassari (A. Farris, G. Sorabba); Divisione di Pneumologia, Ospedale Cervello, Palermo (G. Ferrara, M. Raimondi).

References

study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: Results of a European multicenter trial including 612 patients.


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