Review

Drugs ten years later: Epirubicin

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Introduction

The first clinical report on adriamycin (doxorubicin), the 14-hydroxydaunomycin derivative, dates back to almost a quarter of a century ago [1]. The initial findings [2], indicating a broad spectrum of antitumor activity as well as cardiac effects, were confirmed within a few years in large case series all over the world [3–7]. During the past two decades, doxorubicin represented the single most effective agent in the treatment of breast cancer, malignant lymphomas, bone and soft tissue sarcomas, and an essential component in numerous drug combinations for the management of various neoplastic diseases of adults and children.

The search in experimental animal systems for other anthracycline analogs with better therapeutic index than daunorubicin and doxorubicin has been tenaciously pursued since early 1970s by investigators of Farmitalia Carlo Erba and the Milan Cancer Institute, namely F. Arcamone, A. Di Marco, A. M. Casazza and their coworkers [8–10]. Epirubicin (4'-epiadriamycin, epidoxorubicin, Pharmorubicin*) was the first compound of the new series which became available during the late 1970s for phase I and II studies [11, 12]. In 1984, an international symposium held in Milan [13] concluded that there was preliminary evidence in favor of similar treatment efficacy between epirubicin and doxorubicin but the new analog was moderately less toxic than the parent compound in terms of immediate and delayed side effects.

During the past decade, epirubicin underwent extensive pharmacologic, toxicologic and therapeutic investigations. It is now the proper time to briefly review what has been achieved in terms of pharmacology, optimal dose, schedule, and cost-benefit ratio in the most important human malignancies. Primarily because of space, this review will not attempt to dissect every single study reported in the medical literature. Readers interested in exhaustive details are kindly referred to the recent papers of Mouridsen et al. [14] and Delozier et al. [15].

Preclinical and clinical pharmacology

Chemistry and biochemical reactions of epirubicin

Epirubicin (EPI) is a semisynthetic L-arabino derivative of doxorubicin (DOX) in which the aminosugar daunosamine is replaced by acosamine (Fig.1). The equatorial orientation of the hydroxyl group at the carbon 4' position of the sugar has several consequences on the physical-chemical properties of EPI. In particular, EPI is a weaker base and is more lipophilic than DOX [9]. These features might be relevant to the favorable pharmacological profile of the analog [8,10].

Intercalation of DNA, inhibition of topoisomerase II activity, generation of oxygen and drug free radical, as well as chelation of transition metal-ions are the biochemical reactions most commonly implicated in the mechanism of action and cardiac toxicity of DOX and other anthracyclines [16–19]. Largely, the same reac-

![Chemical structure of doxorubicin (adriamycin) and 4'-epidoxorubicin (epirubicin).](image-url)
tions have also been demonstrated for or are credited to EPI [14, 16, 19]. Here suffice it to say that the steric modification introduced in EPI's structure affects to some degree the stability of DNA-anthracyclines complex [9], causes a faster influx and a lower retention of the analog inside tumor and normal cells [14], determines a different structure of the anthracycline coordination complex with metal ions [8], reduces the ability of the epirubicin-iron complex to peroxidize lipids [20], and favors a unique glucuronidation pathway that is not observed with DOX and other anthracyclines [21]. These biochemical peculiarities may explain the better therapeutic index of EPI than DOX (see below), but do not sustain any substantial difference of the type of reactions implicated in the mechanism of action and toxicity of the analog. It is then not surprising that the two anthracyclines display complete cross-resistance in all in vitro systems [22], and that EPI is also implicated in the phenomenon of multidrug resistance [23].

Pharmacokinetics and metabolism

The pharmacokinetics of EPI after intravenous bolus administration can be fitted to an open three compartment model [24–27]. The comparative analysis of the plasma decay of DOX and EPI consistently show that the analog is more rapidly eliminated than the parent compound. The observation is confirmed not only by the cross-over study performed by Camaggi et al. [24], but also by the more stringent experimental approach with simultaneous administration of the two anthracyclines [26]. While the initial and intermediate half-lives of DOX and EPI are very similar, the terminal half-life is substantially shorter for EPI than for DOX [26]. This difference may be responsible for the lower toxicity, in particular cardiac toxicity, of the analog, and is generally attributed to the unique metabolism of this anthracycline in humans [19]. In fact, EPI is the only anthracycline that serves as a substrate for β-glucuronidation [21]. It is now clear that this metabolic pathway plays a key role in the mechanism of EPI's disposition in humans. According to different authors, the glucuronides of EPI and epirubicinol can account for about one third to more than half of EPI's area under the plasma concentration × time curve (AUC) [25, 26, 28]. Since glucuronidation is a classical pathway of drug detoxification and facilitates the excretion process, the large extent and the inter-individual variability of this EPI's metabolism may bear important consequences on its tolerability in humans.

As already known for DOX, elevated serum bilirubin levels seem associated with very long terminal half lives of EPI and its metabolites [25]. Thus, caution should be used in the administration of EPI to patients with altered liver function, elevated serum bilirubin, and/or liver metastases.

EPI has a wide range of therapeutic doses in humans (50–180 mg/m²). One report in the medical literature [28] suggested that EPI's pharmacokinetics deviated from linearity at very high doses (135–150 mg/m²). This study was not specifically designed to address the question of pharmacokinetic linearity, and according to the authors the observed dose-dependency did not bear a predictive value for more severe acute toxicities. A more recent study [29] has specifically addressed the problem of dose-dependency of EPI pharmacokinetics in the range of 40 to 135 mg/m² in a large patient population. The results indicate that the plasma exposure to EPI and its metabolite is linearly related to the dose.

Clinical toxicology and pharmacology

The spectrum of toxicity associated with EPI is qualitatively identical to that caused by DOX. The most prominent acute side effect is hematological. Nausea and vomiting, hair loss and oral mucositis represent other common side effects [11, 12].

The key point about toxicity in humans is whether EPI is less toxic than DOX as it is in animals. The initial phase I evaluation of EPI defined a range of tolerable doses at 70 to 90 mg/m² every three weeks, and suggested that EPI was better tolerated because it produced less myelosuppression, less nausea and vomiting as well as less hair loss than DOX [11, 12]. Since preclinical studies showed that EPI had a better therapeutic index than DOX [22], the two anthracyclines were administered at equimolar doses to exploit the tolerability advantage of EPI in a subsequent phase II study [30]. In view of the structure similarities of EPI and DOX, this approach led to the conclusion that the two anthracyclines should be used at equal doses on a mg per m² basis. This interpretation did not take into account that the preliminary data of our phase I study fell short of formally defining the maximum tolerated dose (MTD) of EPI [11]. Thus, an appropriate evaluation of the comparative human toxicology of EPI and DOX requires further clarification.

It is now established that the reference dose for the use of EPI as single agent is about 120 mg/m² by i.v. bolus administration every three weeks, while MTD ranges from 165 to 180 mg/m² [31–33]. The administration of EPI at the new reference dose is associated with hematological and extra hematological side effects which are not only qualitatively but quantitatively close to those documented following the administration of 90 mg/m² of DOX every three weeks. At higher doses, oral and intestinal mucositis induced by EPI become frequent and severe enough to concur with bone marrow suppression to the definition of the limiting toxicity [33]. A meaningful comparison of both toxicity and antitumor activity between the two anthracyclines should then take into account whether the doses selected for any given trial are equimolar or equitoxic. When the two drugs are compared at equimolotoxic doses, the incidence and severity of non cardiac toxicities become superimposable [34, 35].
Cardiac toxicity

Preclinical and clinical evaluations of new anthracyclines have traditionally given special emphasis to the problem of cardiac toxicity [7, 36]. Initial studies in animals have indicated that EPI caused similar but less myocardial damage than DOX [22]. The latter observation was actually the major reason for starting the clinical evaluation of the analog.

The clinical experience has confirmed that EPI causes cumulative dose dependent heart failure and cardiac morphological alterations to the myocardium which appear identical to those described for DOX, and mainly consist of dilatation of sarcoplasmic reticulum, myofibrillar loss and interstitial fibrosis [37, 38]. However, a number of reports have now established that the cardiotoxic potency of EPI is significantly lower than that of the parent anthracycline [37-39]. The initial appreciation of EPI's cardiotoxic potential has come from functional studies of left ventricular ejection fraction (LVEF) and electrocardiographic monitoring. These procedures bear low sensitivity and specificity [21] and consequently little value as predictors of subsequent clinical manifestations due to cumulative myocardial toxicity [37].

Morphologic evaluation from endomyocardial biopsies remains the most sensitive, specific and unquestioned method of assessing heart damage by anthracyclines [38, 40, 41]. For doxorubicin, a close similarity exists between the arbitrary dose limitations estimated from morphologic studies and the cumulative dose limits deduced from the prevalence of patients who actually developed congestive heart failure [41]. Two accurate morphologic studies on small series of patients confirmed the lower cardiotoxic potency of EPI compared to DOX [38, 39]. On morphologic examination, the degree of cardiac damage produced by EPI starts to increase with total cumulative doses exceeding 450 mg/m$^2$. These studies concluded that the relative cardiotoxic potency of EPI is about 0.6 of that of DOX. In other words, an equal risk of developing clinical cardiomyopathy is associated with the administration of cumulative doses of 550 mg/m$^2$ of DOX and 900 mg/m$^2$ of EPI, respectively. However, on clinical grounds the 3% probability of developing congestive heart failure is at 450 mg/m$^2$ for DOX and 900 mg/m$^2$ for EPI, respectively [42] (Fig.2). The data on large series of patients would indicate the relative cardiotoxicity of EPI is 0.5 of that of DOX. Thus, the latter figure will be held as the reference equivalence for comparing the clinical cardiotoxic potency of the two anthracyclines.

From our previous discussion on equimyelotoxic doses, the relative myelotoxic potency of EPI is about 0.75 of that of DOX. Taking into account the lower cardiotoxic potency of EPI, the overall toxicological profile in humans indicates that the analog has a limited but significant advantage over DOX. Available data showing comparable antitumor activity of EPI and DOX at equimolar low doses in combination chemo-therapy would then suggest a significantly better therapeutic index for the analog [43, 44]. This conclusion must be accepted with caution in view of conflicting reports from some randomized studies that show equal activity at equimyelotoxic rather than at equimolar doses of the two anthracyclines [34, 35]. The latter studies would support the concept that the better therapeutic index of EPI would be limited only to its comparatively lower cardiac toxicity in humans. Such an advantage could be even greater when this anthracycline is administered concurrently or in sequence with radiotherapy. The cardiotoxic synergism of DOX and chest wall radiation is well known [45, 46]. For EPI, instead, a recent report in patients with small cell lung cancer seems to indicate that such a synergism is not clinically significant even at high cumulative doses (660 mg/m$^2$) of the anthracycline [47].

Clinical activity in various malignancies

Breast cancer

Due to its clinical importance, breast cancer, as in the past acute leukemias and malignant lymphomas, has now become one of the tumor models to test the relative merits of new drugs in solid tumors.

Tables 1 and 2 report the essential therapeutic results of treatments delivered at equimolar or at equimyelotoxic doses when EPI was tested vs DOX either as single agent every three weeks or as part of a drug combination containing fluorouracil and cyclophosphamide (FAC and FEC). The findings showed a discrepancy consistently observed in various clinical trials in which the analog was used at doses ranging from 50 to 90 mg/m$^2$. Although in advanced breast cancer DOX and EPI appeared equally active, the identical
neutropenia was documented. Despite prior DOX myelosuppression was universal and in one patient fatal the starting dose level (110 mg/m\(^2\):1 of 4 patients, 120- median duration of 5.8 months, CR 1) was related to ant to DOX. The overall response rate (62% for a tients previously given DOX but not necessarily resist- high-dose group, Bezwoda et al. [50] treated 18 pa- through low weekly or biweekly doses. Among the as far as acute and delayed toxicity was concerned. [70x229]2, EPI 75 mg/m\(^2\), doses administered (DOX 50 mg/m\(^2\)), [70x253]therapy. The comparative complete plus partial remis- ted FAC and FEC as primary (neoadjuvant) chemother-apy. The response rate was 65% (CR 22.5%) for a five of whom had received prior adjuvant chemotherapy. The response rate was 65% (CR 22.5%) for a median duration of 7 months. Grade 2-3 leukaemia was 35%, congestive heart failure was documented in 2 of 5 patients showing LVEF fall >15%.

Treatment efficacy of low dose epirubicin was evalu- ated in two studies. After the administration of approx-imately 12 mg/m\(^2\)/week, Jones [51] achieved a 43% response rate for about five months. Toxicity was mild and 35% of cases never experienced side effects. Gundersen et al. [52] compared the biweekly infusion of EPI over three hours (50 mg per dose to 68 patients) to the weekly i.v. bolus administration of DOX (20 mg per dose to 81 patients). The response rate was 22% vs. 36% for a median duration of 10 and 9 months, respectively.

In a prospective randomized study, Scottish investi- gators [53] tested ‘low’ (50 mg/m\(^2\)) vs. ‘high’ dose EPI (100 mg/m\(^2\)) every three weeks plus prednisolone (50 mg for five days) in a total of 202 evaluable patients. The response rate and its median duration were superi-or in the ‘high’ dose arm (42% vs. 23% for 7.3 vs. 4 months, respectively); total survival was superim-posable between the treatment groups (10.6 vs. 10.5 months).

At the time of this review, only a few data are avail-able on the efficacy of EPI-containing regimens in an adjuvant situation [54, 55]. At present, the only ran-domized comparison of standard CMF (cyclophospha-
mide, methotrexate, fluorouracil) vs. FEC (fluorouracil, epirubicin, cyclophosphamide) was undertaken by the International Collaborative Cancer Group [54]. In a total of 585 evaluable premenopausal node positive women, the five year results for the entire patient series failed to detect a difference between treated groups. However, there was a superiority of FEC over CMF limited to the subset of women with 1 to 3 positive axillary nodes. Hematological toxicity was about the same in both treatment arms.

**Malignant lymphomas**

During Phase I-II studies in non-Hodgkin's lymphomas (all histologies) refractory to many conventional agents, but not necessarily resistant to DOX, EPI showed a remarkable response rate (58%–75%) in limited case series given 40 up to 180 mg/m² [12, 56, 57]. Of particular interest are the data reported by Case et al. [57]. Nineteen previously treated patients (10 with DOX) were given three dose levels: 120, 150, 180 mg/m². Total response rate occurred in 58% (CR 2) regardless of prior DOX. A >10% fall in LVEF was documented in seven patients, four of whom had previously received DOX.

As far as combination chemotherapy is concerned, the only two randomized studies providing some detailed information are those which tested CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) vs. CEOP, a similar dose regimen substituting EPI for DOX at almost equimolar doses [58, 59]. Al Ismail et al. [58] randomized 50 high grade lymphomas with stage III and IV without detecting significant difference in the comparative complete and partial remission rates, mean duration of response and survival. De Lena et al. [59] included in the study 60 patients (all stages) with 'poor prognosis' and added bleomycin to both regimens as well as radiotherapy to chemotherapy in stages I and II. Tumor response and treatment outcome were essentially the same but decrease in the LVEF was more frequently documented in the DOX-containing regimen. Similar therapeutic results with CEOP in advanced lymphomas with 'poor history' were also reported in 28 patients treated by Comella et al. [60]. More recently, EPI has replaced DOX in various combination regimens, such as MECOP-B [61] and POCE [62], and yielded similar therapeutic results as previously reported for the parent compound.

In Hodgkin's disease, the efficacy of alternating MOPP and ABVD [63] has somewhat delayed the design of new treatment regimens. During the last few years, a novel combination consisting of epirubicin (70 mg/m²), bleomycin, vinblastine and prednisone (EBVP) has been tested by French groups to reduce toxicity. The most recent and documented experience is that reported by Hoerni et al. [64] in 100 consecutive patients with favorable or unfavorable stage I-IIIA. EBVP was delivered in full dosage every three weeks; after the third cycle patients were irradiated. Complete remission before radiotherapy was achieved in 76%. The toxic effects of EBVP also included grade 3 alopecia in half patients. A German group [65] has developed the EBOEP regimen consisting of epirubicin (30 mg/m² on days 1 and 8), bleomycin, vincristine, etoposide and prednisone, all recycled every three weeks. After four cycles followed by radiotherapy, the complete remission rate in 44 patients with stage I-IIIB was 100% with a 3-year relapse free survival of 90% in previously untreated patients. The authors also reported no iatrogenic damage on spermatogenesis. Another three weekly regimen is the Milan VEBEP: etoposide, epirubicin (40 mg/m² on days 1 and 2), bleomycin, cyclophosphamide and prednisone. After eight cycles, radiotherapy is delivered through involved fields (36 Gy). In 43 evaluable patients (stage IIB-IV) the complete remission rate was 95%. With a median follow-up of 12 months, three patients have relapsed. The results of all the above mentioned studies clearly indicate that in Hodgkin's disease EPI can be an effective substitute for DOX in the achievement of complete remission. As of today, the follow-up remains too short to provide meaningful conclusions in terms of curative rate and long-term iatrogenic morbidity.

**Soft tissue sarcomas**

For more than 20 years DOX has been considered the single most effective drug for all histologic subtypes of soft tissue sarcomas [3, 5, 6]. In 1987 the EORTC Soft Tissue and Bone Sarcoma Group [66] has reported the results of a randomized study of DOX vs. EPI delivered at the dose of 75 mg/m² every 3 weeks in a total of 167 evaluable patients. Using equimolar doses the response rate was slightly superior in the DOX-treated group (25%) vs. that of EPI-treated group (18%, P = 0.33), although there was an equivalent time to disease progression (3.5 vs. 3.0 months, respectively). The comparative toxicity showed that leukopenia and hair loss were significantly more pronounced after DOX. In more recent years, EPI replaced DOX in various combination regimens such as those containing ifosfamide, another drug effective in soft tissue sarcomas. The highest response rate was documented in patients given EPI at doses ≥90 mg/m² for a median duration ranging from 4 to 6 months (Table 3). Since in many cases of soft tissue sarcomas the time to achieve the maximum tumor shrinkage is long, and thus requiring high cumulative drug doses, EPI (at the appropriate doses in mg/m²) appears preferable to DOX.

**Lung cancer**

With the exception of the small cell subtype, lung cancer is a group of malignancies which are notoriously chemoresistant to the vast majority of available drugs. Actually, some clinicians are still in doubt whether to treat or not to treat most patients presenting with advanced non-small cell bronchogenic carcinoma.
Table 3. Epirubicin in combination regimens with ifosfamide (IFO) for advanced soft tissue sarcomas.

<table>
<thead>
<tr>
<th>First author</th>
<th>Patients</th>
<th>Dose in mg/m²</th>
<th>CR plus PR (%)</th>
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<tbody>
<tr>
<td>Toma [67]</td>
<td>15</td>
<td>EPI 60–75</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFO 6000</td>
<td></td>
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<tr>
<td>Chevallier [68]</td>
<td>27</td>
<td>EPI 100–130</td>
<td>48</td>
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<tr>
<td></td>
<td></td>
<td>IFO 5000</td>
<td></td>
</tr>
<tr>
<td>Eli [69]</td>
<td>22</td>
<td>EPI 75</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFO 4500</td>
<td></td>
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<tr>
<td>Casali [70]</td>
<td>48</td>
<td>EPI 90</td>
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<td></td>
<td>IFO 7500</td>
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* Dacarbazine.

Reported findings are also often contradictory for a number of reasons, i.e. patient selection and doses of all drugs included in given combination regimens. In this review, we shall concentrate our efforts on a few specific points, namely antitumor activity of EPI as single agent, the feasibility of high doses (i.e. >100 mg/m²) when EPI was delivered alone or in combination, and cardiac toxicity.

In small cell carcinomas, the response rate to EPI as single agent is doubled when the anthracycline is given at doses ranging from 100 to 140 mg/m² [71–74]. When high doses of EPI were delivered, severe granulocytopenia was documented in approximately 80% of patients and hair loss occurred in almost all patients. By contrast, oral mucositis was observed only in a minority of patients (16%) and in no cases was a decline in LVEF > 20% from baseline documented. EPI-containing combinations (with EPI usually delivered at the dose of 50 mg/m²) are yielding a response rate similar to that known for DOX-containing polydrug regimens (Table 4).

In non-small cell carcinomas, single agent EPI yielded a response rate in less than 10% of patients when doses were < 90 mg/m² [75]. When administered at higher doses (105–180 mg/m²), EPI induced a superior response rate (20%–25%) but no complete remissions [33, 76, 77]. Because of poor chemosensitivity of non-small cell carcinomas, also the various drug combinations containing EPI failed to definitely improve total response rate (18%–56%) and median survival duration (5–11 months) over other combination regimens [14].

Pleural mesothelioma

Although the optimal treatment of this malignancy remains to be defined, DOX has been reported among the most effective single agents. Two studies have been recently published in Europe on the efficacy of EPI in advanced mesothelioma. Italian investigators [78] have achieved one partial response in 21 evaluable patients given 75 mg/m². A higher response rate (7 of 48 or 15%) for a median duration of 9 months was reported by EORTC group [79] using the dose of 110 mg/m² every three weeks.

Gastrointestinal cancer

In the various malignancies originated in the gastrointestinal tract (esophagus, stomach, colon-rectum, pancreas and liver) DOX, alone or in combination, has always yielded modest results. The review of the medical literature allows to conclude that, in general, when EPI has replaced DOX the therapeutic results remained superimposable.

The most relevant experience published in esophageal cancer is that of Kolaric et al. [80]. The authors have treated 33 patients combining EPI (150 mg/m² in two days) with irradiation. The overall response rate was 70% (CR 11, PR 12) at the expense of moderate toxicity.

In gastric cancer, single agent chemotherapy with EPI was tested at the dose of 75–100 mg/m² every 3 weeks [14]. Partial response was documented in 17%–27% of cases with a median duration of 3 to 4 months. The administration of EPI through continuous intravenous infusion (6 mg/m² for 3 weeks) has yielded in 27 evaluable patients a response rate of 15% (CR 2) with a median duration of about one year at the expense of minimal toxicity [81]. Table 5 reports the therapeutic results of FEM (fluorouracil, epirubicin, mitomycin C) in advanced gastric cancer. The findings were similar to those reported with FAM, but the authors concurred that FEM was well tolerated.

In colorectal cancer the overall response rate following EPI alone (75–150 mg/m²) was less than 20% [14]. The drug (20 mg/m²/week) was also combined with other agents such as methotrexate, fluorouracil and folinic acid [86]. In 90 patients the response rate was

Table 3. Epirubicin in combination regimens with ifosfamide (IFO) for advanced soft tissue sarcomas.

<table>
<thead>
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<th>CR plus PR (%)</th>
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<td>15</td>
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<td>IFO 4500</td>
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<tr>
<td>Casali [70]</td>
<td>48</td>
<td>EPI 90</td>
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<td>IFO 7500</td>
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* Dacarbazine.

Table 4. Epirubicin in untreated small cell lung cancer. Cumulative data from representative studies.

<table>
<thead>
<tr>
<th>EPI as single agent</th>
<th>No. cases</th>
<th>CR %</th>
<th>CR+PR %</th>
<th>Median survival (mo)</th>
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<tbody>
<tr>
<td>doses &lt;100 mg/m²</td>
<td>101</td>
<td>4</td>
<td>21</td>
<td>4–15</td>
</tr>
<tr>
<td>doses 100–140 mg/m²</td>
<td>155</td>
<td>11</td>
<td>48</td>
<td>7–18</td>
</tr>
<tr>
<td>EPI-containing combinations</td>
<td>419*</td>
<td>30</td>
<td>82</td>
<td>10–18</td>
</tr>
</tbody>
</table>

* Case series with >50 evaluable patients.

Table 5. Fluorouracil, epirubicin and mitomycin C (FEM) in advanced gastric cancer.

<table>
<thead>
<tr>
<th>First author</th>
<th>Patients</th>
<th>CR + PR %</th>
<th>Median survival (mo)</th>
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<tbody>
<tr>
<td>Flechtner [82]</td>
<td>25</td>
<td>28</td>
<td>5.3</td>
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<tr>
<td>Queisser [83]</td>
<td>29</td>
<td>28</td>
<td>6.2</td>
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<tr>
<td>Iton [84]</td>
<td>12</td>
<td>25</td>
<td>6.3</td>
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<tr>
<td>Roth [85]</td>
<td>39</td>
<td>33</td>
<td>5.3</td>
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29% (CR 6%). However, it is difficult to dissect in this study the real contribution of EPI.

In pancreatic cancer, EPI alone at doses ranging from 60 to 90 mg/m² yielded a response rate of less than 10%. Wils [87] reported complete and partial remission in 25% of cases given EPI at 120 mg/m² every 4 weeks. The EORTC group documented partial response in 12% to 14% of cases when EPI was combined with either fluorouracil [88] or ifosfamide [89].

In advanced hepatocellular carcinoma single agent EPI (75–90 mg/m²) yielded a response rate ranging from 9% to 17%. No definite improvement was observed following hepatic intra-arterial infusion at 40 to 90 mg/m² every 3–4 weeks [90].

Head and neck cancer

With the exception of undifferentiated nasopharyngeal cancer, DOX has never been reported to be particularly active in head and neck cancer. The same applies to EPI. In particular, in 27 patients given 75 mg/m² every three weeks Hu et al. [91] have documented a response rate of 52% (CR 6). EPI was also delivered through various combination regimens, the most important of which is that reported by the Institut Gustave Roussy [92]. The regimen BEC (bleomycin, epirubicin (80 mg/m²), cisplatin) induced a 78% complete plus partial response in 47 evaluable patients (27 previously treated with chemotherapy) presenting with advanced disease. As neoadjuvant chemotherapy, BEC achieved a 98% total response with 63% complete remission in 51 patients. Of interest, after a mean follow-up of 19 months, 42 patients (78%) remain alive and disease free. Grade 3-4 hematologic toxicity was observed in 32% of cases after the third cycle. In the ongoing study at the Milan Cancer Institute after primary chemotherapy with EPI (70 mg/m²) plus cisplatin (100 mg/m²) we have documented response in 17 of 21 patients (CR 4).

Ovarian cancer

Single agent EPI (75–150 mg/m²) in advanced ovarian carcinoma refractory to a number of first line regimens with or without cisplatin yielded objective tumor response in about 20% of cases [14]. Probably due to patient heterogeneity, a dose-response effect could not be assessed. Table 6 summarizes the response rate in four patient series treated with EPI and cisplatin. The results are roughly similar to those being achieved with cisplatin plus cyclophosphamide. Furthermore, in two series randomizing EPI vs. DOX [95, 96] treatment findings were almost superimposable. However, less frequent cardiac effects were reported in the EPI treated group.

Prostatic carcinoma

In this disease the response to chemotherapy is notoriously difficult to assess in most patients. Furthermore, the National Prostate Cancer Project (NPCP) classifies stabilization as favorable response. EORTC investigators have tested EPI weekly (12 mg/m²) in 33 patients refractory to endocrine therapy. The response rate was 12% according to the WHO criteria and 54% according to the NPCP criteria, respectively [97]. In a prospective randomized study, Tveiter et al. [98] compared estramustine phosphate (280 mg twice daily) vs. EPI (20 mg/week) either alone or combined with medroxyprogesterone acetate (1000 mg/day) in patients resistant to conventional hormone treatment. Patients receiving EPI showed decreased bone pain; EPI plus medroxyprogesterone also showed improved performance status and response duration. Another important study is that of Pummer [99]. Following orchiectomy, 117 patients with stage D disease were randomized to receive flutamide alone or flutamide plus EPI (25 mg/m² for 18 weeks). Combined treatment with EPI significantly improved percent of response, remission duration and total survival.

Transitional bladder carcinoma

The data on the endocavitary administration of EPI are, at present, difficult to assess mainly because of patients and treatment heterogeneity [14]. Single agent intravenous chemotherapy with EPI at 90 mg/m² every three weeks yielded in the EORTC experience a 15% response rate in 33 patients [100]. In the various drug combinations utilized, it is important to quote the five studies in which in the M-VAC regimens EPI substituted for DOX (Table 7). The response rate, ranging from 37% to 83%, probably reflects disease extent prior to chemotherapy. It is important to point out that even when EPI was administered at the dose of 60 mg/m² [105] the frequency of oral mucositis was lower (4%) compared to DOX (27%).
The past decade allows to conclude that in animal consequence, these studies eventually led to a more appropriate use of this anthracycline. As documented for its parent compound, EPI proved to be particularly effective in all stages of breast cancer, malignant lymphomas, bone and soft tissue sarcomas, undifferentiated nasopharyngeal carcinoma and small cell lung cancer. No consistent benefit could be demonstrable in malignancies usually resistant to doxorubicin such as intestinal and renal carcinomas.

It is well known that the prolonged administration of doxorubicin is limited by cumulative dose-dependent chronic cardiotoxicity. Several approaches have been proposed to reduce the myocardial injury. The use of potentially cardioprotective measures such as delivery of vitamin E, N-acetylcysteine, a bispiperazinedion as ICRF-187, and even liposomal encapsulation of DOX have been shown to decrease the cardiotoxicity in experimental animals and in humans [112]. However, present data have not been sufficiently promising to warrant their large scale clinical application. Thus, empiric dose restriction not to exceed 450 mg/m^2 is still widely practiced to limit within 3% the risk of symptomatic left ventricular or biventricular failure. In fact, the incidence of congestive heart failure raises steeply after higher cumulative doses.

As far as epirubicin is concerned, published data indicate that this analog produces less severe morphologic and functional changes in the myocardium than does doxorubicin. This represents a major advantage since modern chemotherapy is frequently delivered with curative intent. Cumulative doses of EPI above 900 mg/m^2 potentiate a considerable risk of cardiotoxicity and death from congestive heart failure but there is a minimal risk of developing heart failure when patients are given EPI at cumulative doses of 450 to 900 mg/m^2 (see Fig.2). Since subclinical myocardial damage has been documented at doses in excess of 450 mg/m^2 [38], the cumulative safe dose of EPI should not exceed this value in an adjuvant or neoadjuvant situation and when radiation therapy to mediastinum or left breast is part of the sequential combined modality strategy. Although LVEF is probably the most reliable non invasive method to measure the myocardial contractile function, the clinical implications of its changes after anthracycline therapy are still controversial because of rather low sensitivity and specificity in predicting congestive heart failure [37,112]. Radionuclide ventriculography should be obtained as part of the diagnostic work-up before delivering the drug in patients clinically suspected of cardiac disease and when the clinical situation requires the administration of EPI at cumulative doses higher than 450 mg/m^2.

A key point in the clinical management with EPI is its optimal dose regimen, particularly in untreated ambulatory patients with no prior extensive irradiation and/or age less than 65 years. When administered as single agent chemotherapy, 110 to 120 mg/m^2 can be delivered in a standard every three week schedule. This dose is approximately the equivalent of 90 mg/m^2 of DOX. Higher doses could be reserved to carefully treat the above mentioned conceptual evolution in the medical treatment of cancer has profoundly influenced the concurrent clinical development of epirubicin. In fact, the first generation of trials was based upon doses defined in 1979 and 1980 when dose escalation during phase I studies was discontinued at 90–100 mg/m^2, i.e. in accordance to the safety criteria adopted at that time for ambulatory treatment without intensive monitoring of patients. Early in 1980s, the analog was more frequently compared to doxorubicin on equimolar rather than on equimyelotoxic bases. The redefinition of maximal tumor dose according to modern concepts of acceptable risks and manageable complications allowed to initiate a number of new studies with epirubicin. As a consequence, these studies eventually led to a more appropriate use of this anthracycline.

The review of representative medical literature of the past decade allows to conclude that in animal models as well as in various malignancies of adults epirubicin possesses a broad spectrum of antitumor activity as doxorubicin but a reduced potential for cardiotoxicity. As documented for its parent compound, EPI proved to be particularly effective in all stages of breast cancer, malignant lymphomas, bone and soft tissue sarcomas, undifferentiated nasopharyngeal carcinoma and small cell lung cancer. No consistent benefit could be demonstrable in malignancies usually resistant to doxorubicin such as intestinal and renal carcinomas.

**Table 7. M-VAC-like regimens containing epirubicin in advanced transitional bladder cancer.**

<table>
<thead>
<tr>
<th>First author</th>
<th>EPI mg/m^2</th>
<th>Patients evaluable</th>
<th>Disease extent</th>
<th>CR + PR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rüther [101]</td>
<td>30</td>
<td>58</td>
<td>Locally advanced and disseminated</td>
<td>72</td>
</tr>
<tr>
<td>Frassoldani [102]</td>
<td>30</td>
<td>23</td>
<td>Locally advanced</td>
<td>83</td>
</tr>
<tr>
<td>Goldfarb [103]</td>
<td>50</td>
<td>43</td>
<td>Locally advanced and disseminated</td>
<td>72</td>
</tr>
<tr>
<td>Lorusso [104]</td>
<td>30</td>
<td>16</td>
<td>Disseminated</td>
<td>37</td>
</tr>
<tr>
<td>Passalacqua [105]</td>
<td>60 vs 54</td>
<td>DOX 30</td>
<td>Locally advanced</td>
<td>44</td>
</tr>
</tbody>
</table>
selected hospitalized patients. In a combination regi-
men including other myelosuppressive drugs the opti-
mal dose of EPI is 75 mg/m² in ambulatory patients. 
Prestumably, since also peak plasma levels have an im-
portant relationship to both DOX and EPI cardiotoxic-
ity, the standard dose of 110 to 120 mg/m² should be probably be divided in two to three fractions. As pre-
viously demonstrated for DOX, administration of EPI
by prolonged intravenous infusion (48 to 96 hours) can be relatively cardiac sparing. Also the weekly drug
administration (20—25 mg per patient) can be minimal-
ly toxic to the bone marrow without decreasing signifi-
cantly its antitumor activity. Prolonged infusion and
weekly administration can be reserved to elderly pa-
tients, in the presence of reduced marrow reserve from
prior radiation or chemotherapy as well as in the pres-
ence of impaired liver function.

In conclusion, epirubicin is a steroisomer of doxo-
rubicin which retains broad antitumor activity but, at
equimolar doses, is a less toxic compound with regard
to both general toxicity and cardiac injury. Thus, in
future studies there is the possibility for further refine-
ments in developing other anthracycline analogs with
improved cost-benefit ratio, particularly as far as
potential cardiac damage is concerned. Preclinical and
clinical studies have indicated that this can be possible
by structural alterations of the anthracycline molecule.

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