VI Seminario Nazionale per Dottorandi in Farmacologia e Scienze Affini
Siena, Certosa di Pontignano, 2 3- 26 Settembre 2002

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS OF THE ANTHRACYCLINE ANTIBIOTICS IN ADVANCED BREAST CANCER

Fogli S., 4° anno di corso del Dottorato in Farmacologia e Chemioterapia, XIV ciclo. Durata del Dottorato in anni: 4. Sede di servizio: Divisione di Farmacologia e Chemioterapia; Dipartimento di Oncologia, dei Trapianti e delle Tecnologie Avanzate in Medicina; Università di Pisa; Via Roma, 55, 56126 Pisa

The anthracycline glycoside antibiotics are a group of potent anticancer agents representing the mainstay of a large number of clinical protocols for the treatment of advanced breast cancer. Their clinical activity is limited, however, by acute myelosuppression and cumulative dose–dependent, congestive cardiomyopathy. The occurrence of toxicity displays a marked interindividual variation, and for this reason, the incorporation of the analytical pharmacology in the design and analysis of the regimens under investigation may help us to better understand mechanisms responsible for the variability in drug toxicity. On the basis of these premises, our studies were oriented to a pharmacological investigation of epirubicin and idarubicin administered to patients with advanced breast cancer. In particular, pharmacokinetic-pharmacodynamic analysis of epirubicin was performed in patients receiving gemcitabine 1000 mg/m^2 by 30-min i.v. infusion, followed by epirubicin 90 mg/m^2 i.v. bolus and paclitaxel 175 mg/m^2 by 3 h i.v infusion (GEP, n=15 patients). Data were compared with those obtained from patients given epirubicin followed by paclitaxel (EP, n=6) and patients administered with epirubicin followed by paclitaxel 24 h later termed "epirubicin alone" for pharmacokinetic purpose (n=6). High-dose idarubicin at 40-70 mg/m^2 by 48-h infusion with peripheral blood progenitor cells (PBPC) transplantation was given to metastatic breast cancer patients with stable disease or in partial response after 6 courses of GEP combination. Epirubicin-epirubicinol and idarubicin-idarubicinol plasma, renal and cerebrospinal fluid levels were measured by a sensitive reversed-phase high performance liquid chromatography (Fogli S, et al. Ther Drug Monit 1999; 21:367-75) and concentration-time curves were modeled by the MW/PHARM software. Parameters of drug and metabolite exposure were related to hematologic toxicity by a sigmoid-maximum effect (E_{max}) model. Concerning GEP study, we demonstrated that paclitaxel administration significantly increased epirubicinol AUC from 357 ± 146 (E) to 603 ± 107 (EP) and 640 ± 81 h×ng/ml (GEP), and reduced the renal clearance of epirubicin and epirubicinol by 38.0% and 52.2% and 34.5% and 53.0% in GEP and EP-treated patients, respectively, compared to epirubicin alone. Gemcitabine had no apparent effect on paclitaxel and epirubicin pharmacokinetics and renal clearance of epirubicin and epirubicinol. The only pharmacokinetic/pharmacodynamic relationship observed was between neutropenia, as decrease in neutrophil count, and the time spent above the threshold plasma level of 0.1 µmol/l ($tC_{0.1}$) of paclitaxel, with the time required to obtain a 50% decrease in neutrophil count (Et_{50}) of GEP being 7.8 h, similar to that of EP. The clinical pharmacokinetics of high-dose idarubicin was characterized by a dose-proportional increase in plasma dispositions of parent drug and metabolite, with C_{max} and AUC values changed in the range of 7.7-14.8 ng/ml, 26.3-47.4 ng/ml, 423.2-2,581 h×ng/ml and 732.8-4,590 h×ng/ml for idarubicin and idarubicinol, respectively. On the contrary, CSF levels changed independently to drug dose with maximum values of 1.3 ± 1.0 and 1.7 ± 0.8 ng/ml for

idarubicin and idarubicinol, respectively, at 60 mg/m^2. The E_{max} pharmacodynamic model provided a good correlation (r^2=0.74-0.93) between C_{max} and AUC of parent drug and metabolite and the time to engraftment as absolute neutrophil count more then 500/mm^3. Finally, residual idarubicinol levels at the time of PBPC transplantation (144-264 hours) from 1.3 to 13.3 ng/ml affected the time to engraftment most probably by reducing the number of circulating CD34+ cells given. Overall, data of the studies presented here, highlights the relevance of clinical pharmacology in the design and analysis of anthracycline-based regimens.

SIF – Società Italiana di Farmacologia
http://farmacologiasif.unito.it