The European Paediatric Oncology off-patent medicines Consortium (EPOC) - PK-PD trial for Doxorubicin as proof of concept

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Background

Rationale

Doxorubicin (DOX) is a key component of a number of regimens used in the treatment of paediatric cancers and leukaemia. DOX represents old and effective anticancer drugs with a lack of pharmacological data for children. The standard treatment regimens developed are more or less empirical. DOX therefore represents a classical problem in paediatric oncology.

Methods

In recent years we have run therapeutic drug monitoring programs for old but still widely-used cytostatics. For DOX about 140 plasma samples were obtained. Samples were collected 0.5 or 3.9h after the start of a 4h infusion from 30 children with neuroblastoma (age range: 6 month to 14 years) and were analysed by capillary electrophoresis. The standard dose of 30mg/m² BSA was recalculated according to BMI in 2 patients ≤ 1 year. On the basis of published PK data in adults (Eksborg et al. 1985), we performed simulations of the concentration-time curves of the paediatric dosing regimen used and compared these with observed plasma-concentrations.

Results and conclusion

• Clinical trials to establish age dependent pharmacokinetic data are urgently needed to give more precise dosing recommendations
• Structures to investigate the age dependent PK of generic drugs in infants and toddlers are needed

EPOC

The EPOC consortium obtained funding within the 7th framework program of the EU to set up a network to perform paediatric oncology pharmacology trials with a special focus on infants and toddlers. The consortium consists of participants from 4 countries; Germany, England, France and Italy. The first and “proof of concept” trial of the new concept will be on doxorubicin.

Since almost all paediatric oncology patients are treated within national or European therapy trials, the EPOC pharmacology studies will be designed as Add-on trials to these studies. Collaborations with the chief investigators of the latter studies will be established in order to allow access to the relevant clinical data for each patient without the need for parallel, duplicate investigations.

Challenges

• variety of treatment regimens and dose schedules
• limitations in volume and number of blood samples
• pre-analytical problems especially in the very young
• evaluation of toxicity: surrogates or decades of follow-up
• transfer of data into clinical practice

Doxorubicin trial

• 100 Patients < 18 years (with an even distribution of patient ages across age ranges)
• eligible patients must be enrolled in a national or European protocol for treatment of:
  - Wilms tumour
  - Neuroblastoma
  - Soft tissue sarcoma
  - Ewing sarcoma
  - Acute lymphoblastic leukaemia
• treatment with doxorubicin will be done according to the respective protocol
• for each patient PK/PD will be analysed on two different doxorubicin administrations
• more sparse plasma samples will be collected in younger children
• PK parameters, will be determined using population pharmacokinetics by nonlinear mixed-effects modelling (NONMEM)
• maturic peptide BNP, the precursors NT-proBNP and NT-proANP, as well as cardiac troponin T will be measured in plasma to evaluate their use as clinical markers for cardiotoxicity
• the impact of pharmacogenetic variability on the clearance of doxorubicin will be explored
• long term toxicity can later be correlated to concentrations of biomarkers and to individual drug exposure of the patients (AUC for doxorubicin and doxorubicinol)
• planned start: January 2010
• number of centers: 12-18

Contact and Acknowledgement

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