List of most frequent Adverse drug reactions in paediatric oncology

Workshop pharmacovigilance in the paediatric population
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Pharmacovigilance in paediatric oncology?

- Full-text search in the journal of the International Society of Paediatric Oncology (SIOP) “Pediatric Blood and Cancer” (1975-2014):
  - 7 x “pharmacovigilance”
  - 8 x “pharmacoepidemiology”
  - 1 case report: “A Naranjo algorithm to determine a level of causality of omeprazole was applied and a score of 8 was obtained, suggesting a “probable” causality of adverse drug reaction” (hemifacial paralysis – proton pump inhibitor – 13 y male with leukaemia)

- However, many activities and publications on drug safety
Observational studies in paediatric oncology

- PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup, PanCareLIFE, PanCare – EU FP funded)
  - Case-control studies, risk estimates, follow-up recommendations
- Late effects surveillance system (DE), likely similar other countries
  - Follow-up recommendations, documentation of patients after end-of-trial
- Children’s oncology group (COG, US)
  - Survivorship guidelines = follow-up recommendations
- Childhood Cancer Survivor Study (CCSS, NIH/St Jude, US)
  - Cohort of >20000 affected children (diagnosis 1970-1986), siblings, ...

Medicine use in paediatric oncology

• Medicines given usually at „maximum tolerated dose“
  – Dose with which unacceptable toxicities occurred in less than e.g. 33% pts
• Most medicines are cytotoxic
  – General toxicities (suppression of tissue regeneration)
  – Specific toxicities
• Cytostatic and targeted medicines have also (unacceptable) toxicities
  ➔
• Commonly occurring (expected) ADRs are documented individually
• Reporting and monitoring of ADRs not comprehensive
• Interest in unexpected ADRs, high-risk medicines, evolving, learning
Pharmacovigilance by paediatric oncologists

• Variable organisation
  – „Clinical trial safety desk“ (e.g., EURAMOS)
  – Contact person for paediatric cancer-drug safety at national level (across clinical trials)
  – Issue to collect, merge, analyse data from trials, off-label use etc.
  – Interest in specific drug safety, e.g. indication, genetics, new medicines

• Common coding dictionary: CTCAE (NCI, US)
  – Conversion table to MedDRA available
ADRs in paediatric oncology

- Deemed acceptable if readily manageable (reversible), e.g. by
  - Symptomatic treatment
  - Stopping / reducing / slowing administration
  - Stopping / replacing medicine

- Of highest concern are ADRs that are
  - Acutely life-threatening (infections, septic shock, renal failure, tumour lysis)
  - Disabling or life-threatening (heart failure, atherosclerosis, osteonecrosis)
  - Impairment of intellectual, psychosocial, physical development
  - A second malignant neoplasm (attributable to medicine)
  - Infertility; need for continuous medication; ...
EMA Comparison paediatric – adult ADR profile

- Search of primarily paediatric literature, research, experience (not EPARs, not labels, incomplete adult data)
- Document drafted (acknowledgments to Alessandro Jenkner), not yet reviewed, not yet available
- Combinations (42) of medicines and known risks (not haematological)
- Assumptions on occurrence in paediatric (P) vs. adult (A) population:
  - Combinations: 21 P>A, 8 P<A, 3 P=A, 10 unknown relation
  - Some suggested assumptions will be interesting to check (example)
  - Some literature-generated assumption appear not plausible
  - For some ADRs, other age categories relevant
Comparison ADR profiles – examples

• P>A
  - Neurotoxicity (stroke-like, seizures) / ifosfamide
  - Veno-occlusive disease / thioguanine
  - Growth suppression / prednisone, imatinib
  - Lung toxicity / bleomycin
  - Haemorrhagic pleural effusions / e.g. imatinib
  - ? irreversible ototoxicity / cisplatin

• P<A
  - Differentiation syndrome, QTc prolongation / arsenic trioxide
  - Hepatic fibrosis, cirrhosis / methotrexate
  - Pancreatitis, neurotoxicity / asparaginase
  - Interstitial lung disease / gefitinib
  - ? cerebellar toxicity (ataxia, slurred speech) / cytarabine
Example: data in EudraVigilance

- Literature-generated assumption: “bleeding and thromboembolic events after bevacizumab observed only in adults”
- Standard MedDRA Query (SMQ) available for cardiovascular reactions
- Bevacizumab has been, is in paediatric trials and is used off label
- Others inhibitors of angiogenesis (ATC = L01XE): ponatinib, pazopanib, vandetanib, sunitinib, ...
- Collaboration between EMA teams, in order to explore available data (Acknowledgements to Gianmario Candore, Francois Domergue)
Example: data in EudraVigilance (cont.)

- Cases of thromboembolic embolic events also signalled in children
- Limited data for quantitative comparison between children and adults
- Further exploration (details, age, survival time, co-medication)
- Generation of evidence for management? prevention?
Example for post-authorisation study in paediatric oncology

Particular cause for concern

→ post-marketing authorisation safety studies and/or risk management system can be required as condition of authorisation

= legal provision in

Paediatric Regulation (EC) No. 1901/2006, Article 34 (2)
Example: CHMP outcome

Data from studies and concerns in PIP

→ Obligations for paediatric indication

→ Identification of missing data and related activities
Conclusions

• Paediatric oncology may be a worthy and interesting field for safety monitoring because medicines are expected to result in ADRs
• Indications (use) in children are different from that in adult cancers
• Novel toxicities (e.g., found in animal studies) to be monitored
• Paediatric oncology: most patients are in clinical trials (favourable for understanding safety and for protecting children), with many medicines used off label („standard of care“)
• Reports from paediatric oncology (Article 45) and first PIP results ➔ EPARs of about 15 anti-cancer medicines updated
• Publications and ADR data / safety profile may differ
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