EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

~~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, …

http://www.pancaresurfup.eu/, http://www.less-studie.de/,
http://survivorshipguidelines.org/, https://ccss.stjude.org/

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.)

Population	Exposure	**TE cases**	All cases	PRR estimate	PPR 2.5% quintile
Paediatric	**Bevacizumab**	10	151		
Paediatric	Any other	6940	313388		

- 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)

2.1.4. Studies

Area	Number of studies	Description
Quality	0	Not applicable.
Non-clinical	0	Not applicable.
Clinical	3	Study 1: Open-label, multi-centre, non-randomised, dose-escalation trial to evaluate safety and efficacy of chemotherapy, haematopoietic stem cell transplantation and imatinib in children from 1 year to less than 18 years (and young adults) with acute lymphoblastic leukaemia. Study 2: Open-label, multi-centre, randomised trial to evaluate safety, activity and efficacy of imatinib on top of chemotherapy and in combination with haematopoietic stem cell transplantation in children from 1 year to less than 18 years with acute lymphoblastic leukaemia. Study 3: Development and validation of an integrated physiology-based pharmacokinetic (PBPK) and population pharmacokinetics model.

Concerns on potential long term safety issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By June 2011
Deferral for one or more studies contained in the paediatric investigation plan:	No

It is considered that the following issues are particular causes of concern in children:

- Growth, sexual maturation, fertility, haematologic and biochemical laboratory changes, and second malignancies.
- Pharmacokinetic data and dosing information in children younger than 5 years of age (Update and

Example: CHMP outcome

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To conduct an observational registry collecting efficacy and safety data in newly diagnosed paediatric Ph+ Acute Lymphoblastic Leukaemia (ALL) patients treated with chemotherapy + imatinib ± HSCT. Submission of final study report.	31/12/2020

Important missing information		
Paediatric patients: Long term follow up	Routine pharmacovigilance activities **Additional activities** To obtain long-term follow-up data to assess the effects of treatment, on growth, sexual characteristic acquisition, fertility, hematologic and biochemical laboratory changes and second malignancies as well as pharmacokinetic data in the paediatric population. These measures will be assessed in the CSTI571A2405 study (a registry FUM in CML patients).	Growth retardation in children is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use Relevant preferred terms are reported as AE in SPC Section 4.8 Undesirable effects. Second malignancy is appropriately communicated through current labeling: SPC Section 5.3 Preclinical safety data There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities identify additional data, the risk will be communicated through the labeling and additional risk minimisation activities may be proposed if necessary.

Data from studies and concerns in PIP

→ Obligations for paediatric indication

→ Identification of missing data and related activities

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000406/human_med_000808.jsp&mid=WC0b01ac058001d124

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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