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Patient safety in cancer patients: experiences with trastuzumab

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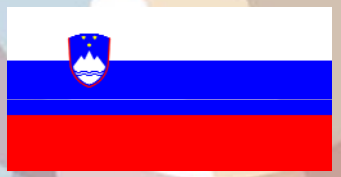


Adverse Drug Reaction (ADR): A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

Unexpected Adverse Drug Reaction:
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

Serious Adverse Drug Reaction is any untoward medical occurrence that at any dose:
- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

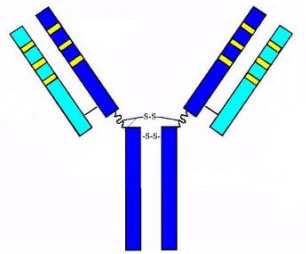
Pharmacovigilance: Greek 'Pharmaco' (medicine) + Latin 'Vigilantia' (vigilance, watchfulness).

It is the process of monitoring, evaluating and improving the safety of medicines in use. It is carried out by pharmaceutical companies on their products and by government agencies on all medicinal products.

Breast cancer in general

- Most common diagnosed cancer in women
- The second leading cause of cancer-related death in women
- Treatment depends on biology of the tumour (e.g. invasiveness, grade of malignancy, hormone dependency, HER status,...)
- Systemic treatment includes chemotherapy, hormone therapy and targeted therapy with new biologicals

Herceptin® - trastuzumab



- Recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2)
- Overexpression of HER2 is observed in 20% - 30% of primary breast cancers
- Trastuzumab inhibits the proliferation of human tumour cells that overexpress HER2
- In Slovenian clinical practice used from 2001 for metastatic treatment and from 2005 for adjuvant treatment of early breast cancer

Trastuzumab adverse drug reaction

Summary of product characteristics:

Adverse reactions attributed to Herceptin in ≥ 10 % of patients in the two pivotal clinical trials	
Body as a Whole	**abdominal pain, asthenia, chest pain, chills, fever, headache, pain**
Digestive	**diarrhoea, nausea, vomiting**
Musculoskeletal	**arthralgia, myalgia**
Skin and appendages	**rash**

Our experiences: high number of reported ADRs

Frequency of adverse reactions

Period	% of adverse drug reactions
12.10 – 29.11.2006	**35,7 % (5/14)**
30.11 – 16.01.2007	**57,1 % (8/14)**
17.01 – 31.03.2007	**37,9 % (11/29)**
01.04 – 18.06.2007	**30,4 % (7/23)**
19.06 – 22.08.2007	**18,2 % (4/22)**
23.08 – 30.11.2007	**16,7 % (5/30)**
Total	**30,3 % (40/132)**

- All reactions at first application
- Most frequent reactions: fever and chills

Retrospective study: use of Herceptin® in practice

JUNE 2007

Present situation

- Reconstitution of Herceptin is done by nurses and takes place on the wards
- Non-sterile conditions
- Dosing regime → as all the patients would have 75 kg
- Application of only full vials (150mg × X)

AIM OF THE STUDY

Identify possible dosing errors and to evaluate costs directly connected with them

Methods

- Computer follow-up of Herceptin (by patients with corresponding doses) → actual doses (1)
- Body weight from patient's medical notes → expected doses (2)
- Comparison of doses (1) and (2)
- Calculate possible dosing errors and savings of trastuzumab (under centralised preparation condition)

Examples from practice

- Patient treated according to 2 mg/kg protocol:
- 60 kg patient → received dose 150 mg (one vial of Herceptin), recommended dose 120 mg.
  Deviation: (150-120)÷120 = **25%**

2. Patient treated according to 6 mg/kg protocol:
- 85 kg patient → received dose 450 mg (three vials of Herceptin), recommended dose 510 mg.
  Deviation: (450-510)÷510 = **(-)12%**

According to data from St. Bartholomew's Hospital London (tertiary centre for cancer services, National Health Service Trust), the allowed deviation from protocol is **±5%.**

Results
Deviations from protocol

Number of patients receiving of Herceptin in June 2007: N = 166	
Deviation from protocol	**Portion of patients with deviated protocol**
Deviation ≥ 10% from protocol	**54% (N=90)**
Deviation ≥ 20% from protocol	**19% (N=31)**
Deviation ≥ 25% from protocol	**8% (N=14)**

Results

Possible savings with centralised preparation
EXAMPLE

On day X we prepare:

- Two solutions for patients on 2 mg/kg protocol, weighting 60 kg and 75 kg and two solutions for patients on 6 mg/kg protocol, weighting 65 kg and 70 kg
- In practise we would use: 150mg + 150mg + 450mg + 450mg = 1200mg
- We should use: 120mg (60 kg) + 150mg (75 kg) + 390mg (65 kg) + 420mg (70 kg) = 1080mg
- **Residue: 1200mg – 1080mg = 120mg → another dose for one 60 kg patient on 2 mg/kg protocol!!!**

Results

Possible savings with centralised preparation

- Using recommended dosing, we would save 1768 mg of Herceptin in June 2007, which accounts for 11 vials
- Taking into account only residuals of whole vials, as the smaller leftovers are thrown away at the end of the day, we would **save 4 vials of Herceptin** in June 2007

- One vial of Herceptin costs 731,41 € → in June 2007 we could have saved 2925,64 €

- Calculating average year consumption, we could have saved **35 107,68 €** in year 2007

Plans for the future

1. **Implementation of centralised chemotherapy production**

2. **HER2 positive breast cancer treatment database** (e-HER2)
   → pharmacovigilance study to:

- follow-up all patients on treatment with Herceptin in routine clinical practice
- following adverse drug reactions (including long-term ADR)
- following routine monitoring of cardiac function
- development of electronic tool to follow-up the effects/results of systemic treatment

THANK YOU FOR YOUR ATTENTION!!!