Update on Drug Hypersensitivity

Desensitization in immediate drug hypersensitivity

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Content

Desensitization in immediate type drug allergy

- Patient: initial reaction and allergologic workup
- What do we mean with „desensitization“ in drug allergy?
  - Nomenclature
  - Concepts on pathophysiology
  - Protocol
- Course of further treatment of the patient
- Conclusions?

Patient C.B.*1961

- Fallopian tube cancer, poorly differenciated (11/2012)
- Paraneoplasitc dermatomyositis
  - Surgery
  - First line chemotherapy with Carboplatin, Paclitaxel (01/2013 – 04/2013)
  - Relapse (7/2015)
  - Second line chemotherapy with Carboplatin, Paclitaxel in combination with methotrexate
    - Severe pancytopenia and mucositis
    - Stop after frist cycle
  - Doxorubicin (09/2015 – 2/2016)
  - Letrozole (03/2016 – 07/2016)

Patient C.B.*1961

- 8/2016: progressive disease with peritoneal carcinomatosis
  - Third line chemotherapy with carboplatin, paclitaxel and Bevacizumab
  - Stop during 3rd cycle (11/2016) due to anaphylaxis grade III (flush, dyspnoea, nausea) during infusion of carboplatin

- Allergology consult

Patient C.B.*1961

- Allergologic workup
  - Pricktests with Carboplatin
    - 0.1 mg/ml, 1 mg/ml, 3 mg/ml, 10 mg/ml: negative
  - Pricktests with Paclitaxel
    - 1 mg/ml, 6 mg/ml: negative
  - Intradermal tests with Carboplatin
    - 0.1 mg/ml, 1 mg/ml, 3 mg/ml: highly positive
  - Intradermal tests with Paclitaxel
    - 1 mg/ml, 6 mg/ml: negative

Hesterberg PE et al. J Allergy Clin Immunol 2009;123:1262-7.

Patient C.B.*1961

- Grade III anaphylaxis during 10th administration of Carboplatin
  - Type I sensitization to Carboplatin in the skintests
  - Premature staging: good response with regression of peritoneal carcinomatosis and regression of tumor markers
- Request for desensitization with Carboplatin

Desensitization in drug allergy

- Induction of a temporary state of clinical unresponsiveness/tolerance to a compound responsible for a DHR
- Repetitive small incremental doses of the drug
- Duration of the tolerance after desensitization
  - Unknown
  - may depend on the type of reaction, the drug, on patient-related factors
  - Needs to be re-introduced each time the drug needs to be given
- Drug tolerance does neither indicate a permanent state nor that the mechanism involved is immunologic tolerance
- ≠ Graded challenge
- "Tolerance induction“, „adaptive desactivation“

Demoly P et al. ICON on drug allergy, Allergy 2014
Cernadas J et al. ENDA-Position paper on desensitization in drug allergy, Allergy 2010

Tolerance induction

- assume IgE-mediated mechanism in our patient
- consecutive administration of suboptimal doses of antigen renders mastcells and basophils unresponsive to the drug
- antigenic determinants bind to IgE on the surface FceRI receptors, but do not cross-link such IgE.
- And/or: induction of rapid internalization of cross-linked antigen receptors, which depletes the cell surface of these receptors
- Decreased levels of signal transducing molecules (Syk, Lyn)
- Naturally occurring Syk-deficient basophils do not degranulate
- STAT-6-deficient mast cells cannot be desensitized
- Stabilization of the antigen-antibody-receptor molecule on the cell surface?

SobotkaAet al. J Immunol 1979;122:511–517. 266.
Shalit M, Levi-Schaffer F. Clin Exp Allergy 1995;25:896–902.
Steinman RM et al.J Cell Biol 1983;96:1–27.
Kepley CL.. Int Arch Allergy Immunol 2005;138:29–39.
Castells M et al. Cancer Immunol Immunother 2012; 61:1575-84

Protocol

Total dose	500 mg	Solution concentration (mg/ml)	Total dose in each solution (mg)
Solution A	250 ml	0.02	5.0*
Solution B	250 ml	0.20	50.0*
Solution C	250 ml	2.00	500.0*

Step	Solution	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose infused
1	A	2	15	0.010	0.010
2	A	5	15	0.025	0.035
3	A	10	15	0.050	0.085
4	A	20	15	0.100	0.185
5	B	5	15	0.250	0.435
6	B	10	15	0.500	0.935
7	B	20	15	1.000	1.935
8	B	40	15	2.000	3.935
9	C	10	15	5.000	8.935
10	C	20	15	10.000	18.935
11	C	40	15	20.000	38.935
12	C	75	184.4	461.065	500.000
			Total time = 5.82 h		Total dose infused = 500 mg*

Castells M et al. Cancer Immunol Immunother 2012; 61:1575-84

Patient C.B.*1961

- 12/2016: target dose 400 mg Carboplatin
  - Step 10: Solution C, 20 ml/h, cumulative dose appr. 10 mg Carboplatin:

    patchy erythema face & hands, flush, generalized erythema, itching, pulmonary opression, PEF - 60%, wheeze, pulse and blood pressure stable
  - Stop infusion, clemastin 2 mg, ranitidine 50 mg, salbutamol, methylprednisolone 125 mg
  - Full recovery within 60 min
  - Restart with adapted protocol:

    solution C, 10 ml/h, 15 ml/h, 20 ml/h, 25 ml/h, 40 ml/h, 75 ml/h
  - Tolerated full dose without further events

Patient C.B.*1961

- 01/2017: target dose 321 mg Carboplatin
  - Step 12: Solution C, 75 ml/h, cumulative dose appr. 25 mg
    Carboplatin: patchy erythema face& hands, flush, generalized erythema, itching, complete nasal obstruction, PEF, pulse and blood pressure stable
  - Stop infusion, clemastin 2 mg, ranitidine 50 mg,
    methylprednisolone 125 mg
  - Adrenaline i.m. 0.3mg
  - prolonged recovery within 90 min
  - Restart with adapted protocol:
    solution C, 20 ml/h < 30 ml/h, 40 ml/h, 50 ml/h, 75 ml/h,
  - Tolerated full dose without further events

Patient C.B.*1961

- 02/2017: target dose 369 mg Carboplatin
  - Step 11: Solution C, 40 ml/h, cumulative dose appr. 14 mg Carboplatin: patchy erythema face & hands, flush, generalized erythema, itching, PEF, pulse and blood pressure stable
  - Stop infusion, clemastin 2 mg, ranitidine 50 mg, methylprednisolone 125 mg
  - prolonged recovery within 75 min
  - Restart with adapted protocol:

    solution C, 10 ml/h < 15 ml/h, 20 ml/h, 30 ml/h, 45 ml/h, 75 ml/h
  - Tolerated full dose without further events

Summary

- Our patient is not really tolerant despite „tolerance induction“
  - Skin test positive <–> IgE-mediated mechanism

- Antiallergic premedication not very useful in our hands
- For select cases with no other good therapeutic alternative only!
- Individual management guided by established protocols
- Mechanism of tolerance induction unclear