Carboplatin Desensitisation

A Case in Progress

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Aims

1. Discuss case of a patient referred ?platinum-chemotherapy anaphylaxis.
2. Explore platinum-based chemotherapy allergy.
3. Explore the concept and process of drug allergy desensitisation.

Case - Background

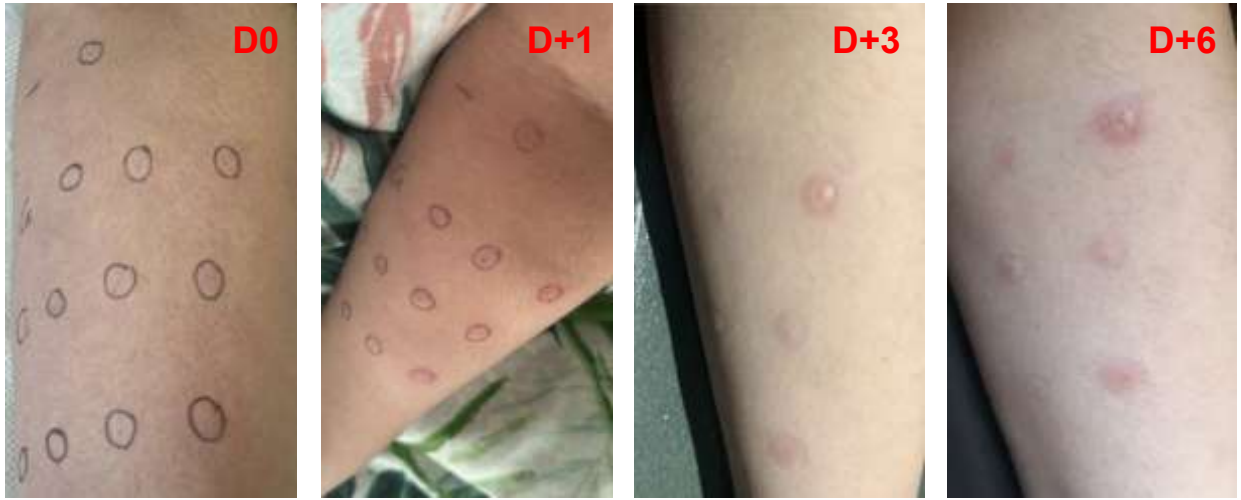
- 43F w/ovarian carcinoma referred to for ?platinum-based chemotherapy allergy +/- desensitisation. No other significant medical history.

- 2021: dx w/ovarian carcinoma in Pakistan. Tx w/3 cycles of 3 weekly carboplatin and paclitaxel. 5 minutes into 9th dose of carboplatin → dizziness, dyspnoea, bradycardia, LoC → ITU admission. Since then no platinum-based drugs but has had paclitaxel on multiple occasions.

- 2025: moved to UK. CUH oncology wishes to restart platinum-based chemotherapy with consideration of desensitisation or alternative drug. Carboplatin, cisplatin, and oxaliplatin available.

Case - Skin Testing

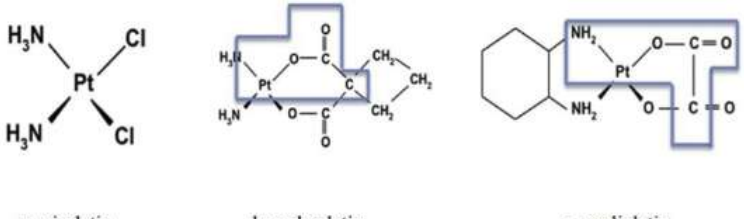
- SPT (neat) + IDT (1:100, 1:10, neat) (based upon n=189 case series; Ramon y Cajal University Hospital, Madrid)
- All negative (though >6 month post reaction; 6/52-6/12 recommended).
- Direct irritant/cytotoxic reaction occurred from neat IDT. Managed with simple analgesia.



Platinum-Based Chemotherapy Allergy

- One of the most common causes of chemotherapy allergy (46% of patients with at least 7 infusions).
  - Other classes of chemotherapy rarely cause allergy, except etoposide/teniposide and asparginase (up to 40% of patients).

- Relatively high rate of cross-reactivity between carboplatin (CA) -oxaliplatin (OX). Cisplatin (CI) allergy and cross-reactivity much rarer. Common epitope the likely cause.



Pasteur et al, 2019

- Retrospective cohort study, Dijon University Hospital (n=155).
- CA/OX allergy common as is cross-reactivity. CI allergy very rare. Sensitisation to CI and others only seen when both agents previously administered.
- No reactions seen when CI initiated in CA/OX allergy in this study. n=4 in older studies had CI reaction post-CA reaction but on review all previously exposed to CI.

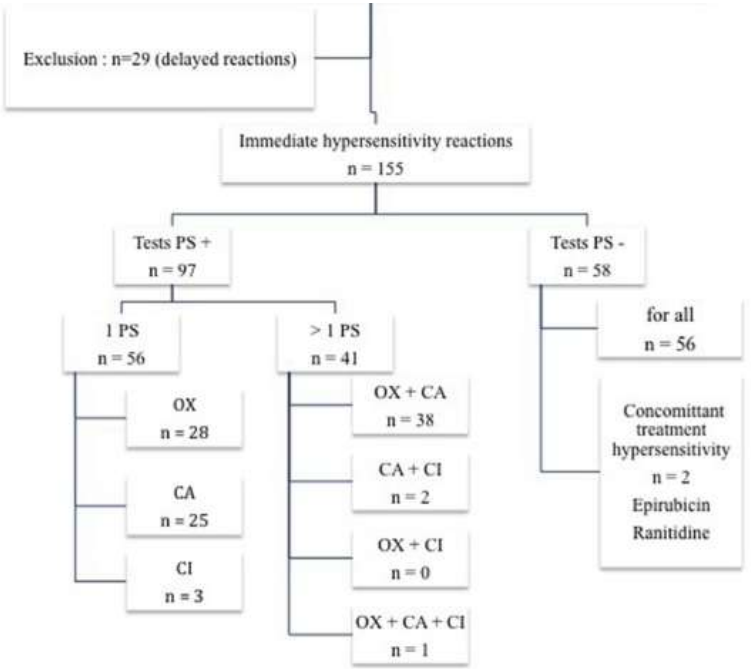


TABLE II. Clinical signs experimented during hypersensitivity reaction with platinum salts in the 155 patients

Clinical signs	Patients, no. (%)
Cutaneous (erythema, pruritus, urticaria, angioedema)	107 (69)
Cardiovascular (chest tightness, tachycardia, blood pressure alterations)	47 (30)
Pulmonary (dyspnea, bronchospasm, desaturation)	18 (12)
Gastrointestinal (nausea, vomiting, diarrhea)	13 (8)
Neurological (paresthesia, malaise, vertigo)	45 (29)

Case - Outcome and Plan

- Test outcome: clinically anaphylaxis to carboplatin though testing negative.
- “Cisplatin/oxaliplatin allergy cannot be excluded without a high-risk challenge. Cisplatin has a lower likelihood of cross-reactivity when compared to oxaliplatin. Choice of future chemotherapy at behest of oncology team as per risk-benefit analysis.”
- “If carboplatin is deemed to have significant superiority as a chemotherapeutic agent, a high-risk desensitisation protocol must be used for every dose.”
- “If cisplatin or oxaliplatin is preferred, then initiation will vary according to the oncology protocol. If a single dose of cisplatin/oxaliplatin is preferred, then it should be given using a high-risk desensitisation protocol. If multiple doses of cisplatin/oxaliplatin are preferred, then a high-risk challenge should be performed in the first instance.”
- “Discharge from allergy. We are happy to be contacted with regards to desensitisation/challenge protocols if this is required in the future.”

Drug Desensitisation

- Multiple small doses in rapid succession can result in a target dose being given without a reaction. This can be used to give a drug when alternatives are not viable.

- Has been used successfully in IgE-mediated allergy, MRGPRX2-mediated pseudoallergy, NSAID pseudoallergy, and low-risk T-cell mediated reactions.

- Unlike peptide immunotherapy, e.g. pollen, tolerance is temporary. Without regular doses, tolerance will be lost in hours/days. Often necessitates desensitisation before each dose.

- Protocols typically takes 4-12 hours.

Mechanism

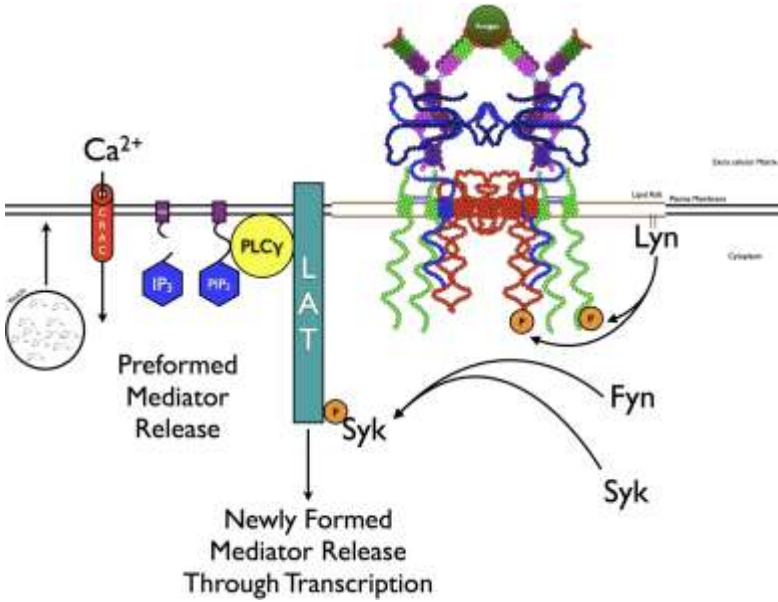
Classical IgE-mediated Mast Cell Degranulation:

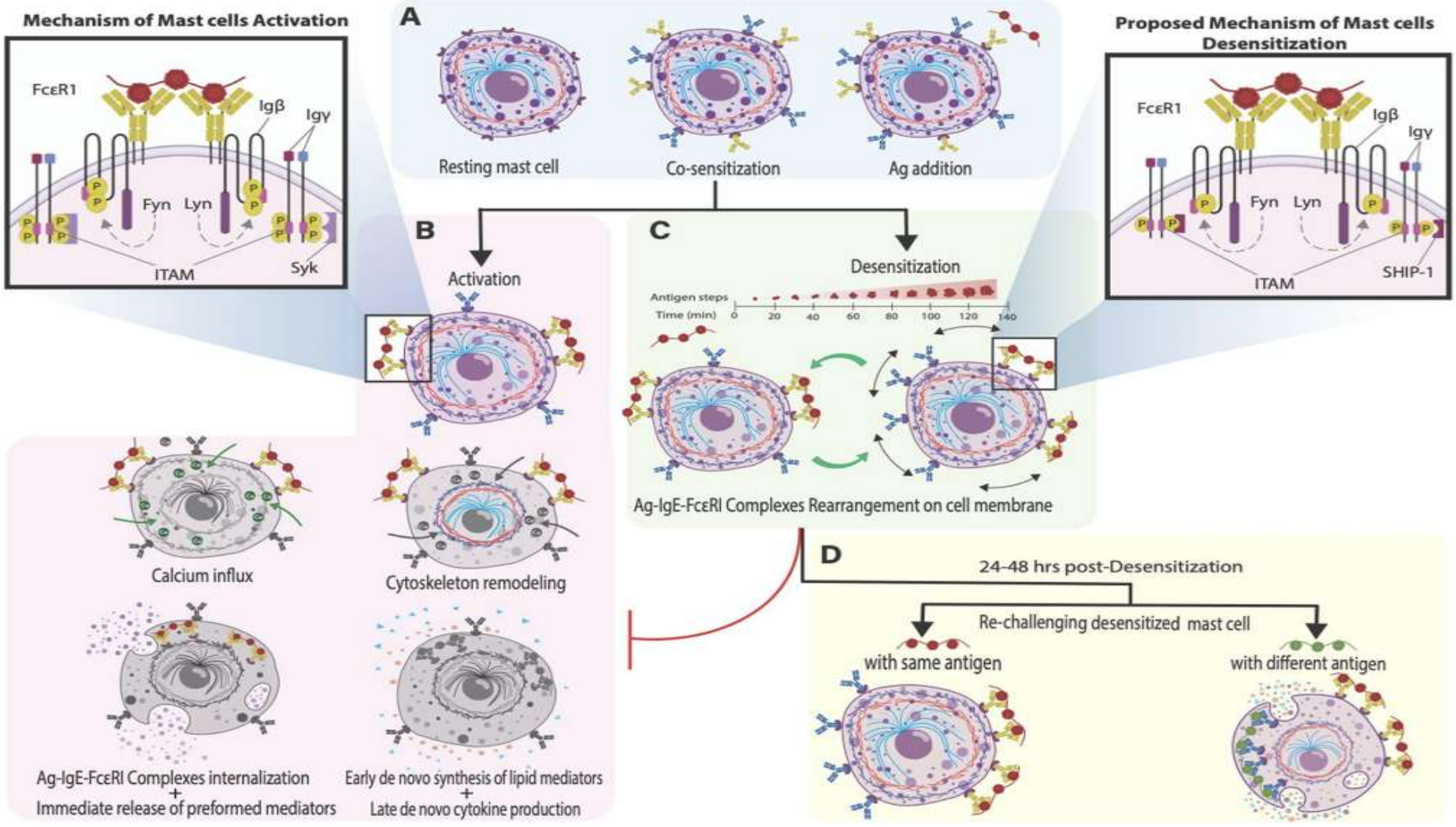
1. IgE-FCεRI cross-linking
2. Lyn kinase phosphorylates immunoreceptor tyrosine-based activation motifs (ITAMS) on β/γ chains.
3. Phosphorylation of Syk kinase
4. Phosphorylation of LAT
5. Activation of IP3 signalling pathway → calcium influx
6. Cytoskeletal remodelling
7. Degranulation/production of new mediators.

Desensitiation of IgE-mediated Mast Cell-dependent Allergy:

- Incremental addition of allergen at fixed time intervals forms small clusters of activated receptors on the surface. This appears to activate immunoreceptor tyrosine based inhibition motifs (ITIMS) → activate SHIP-1 → dephosphorylates Syk preventing downstream calcium influx.

Mechanism of desensitisation in non-IgE-mediated allergy is unclear.




Mechanism of Mast cells Activation
FcεR1
Igβ
Igγ
Fyn
Lyn
ITAM
Syk
A
Resting mast cell
Co-sensitization
Ag addition
Proposed Mechanism of Mast cells Desensitization
FcεR1
Igβ
Igγ
Fyn
Lyn
ITAM
SHIP-1
B
Activation
Calcium influx
Cytoskeleton remodeling
Ag-IgE-FcεRI Complexes internalization
+
Immediate release of preformed mediators
Early de novo synthesis of lipid mediators
+
Late de novo cytokine production
C
Desensitization
Antigen steps
Time (min) 0 20 40 60 80 100 120 140
Ag-IgE-FcεRI Complexes Rearrangement on cell membrane
D
24-48 hrs post-Desensitization
Re-challenging desensitized mast cell
with same antigen
with different antigen

IgE-mediated Drug Allergy Desensitisation

- Protocols vary and starting dose can range from 1/10,000th to 1/100th of a full dose often followed by 12 steps of slowly increasing doses.
- IV line and continuous monitoring is obligatory.
- Using pre-existing published protocols is recommended however if none exist, BSACI has an IV desensitisation protocol calculator developed at Brigham and Women's Hospital, Boston.
- Breakthrough reactions most often occur in the first course and in subsequent procedures become less severe. There is no common approach as to whether to stop or push through once patient is stable. 33% have a reaction, most of which are mild.
- Pre-medication not recommended as may mask early symptoms, resulting in moving to the next step leading to a worse reaction.

Example Desensitisation Protocol

Desensitisation calculator

Name of patient: NHS number:
Name of clinician: GMC number:
Name of medication:
Final dose: mg
Protocol: 3-bag
Bagsize: ml

Calculate | Clear

Description of 16-step protocol

Name of medication: **Carboplatin**

		Concentration	Total mg per bag	Amount of bag infused (ml)
Solution 1	250 ml of	0.0037352 mg/ml	0.9338	1.875
Solution 2	250 ml of	0.037352 mg/ml	9.338	3.75
Solution 3	250 ml of	0.37352 mg/ml	93.38	7.5
Solution 4	250 ml of	3.7234 mg/ml	930.85	250

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	0.5	15	0.125	0.0004669	0.0004669
2	1	1	15	0.25	0.0009338	0.0014007
3	1	2	15	0.5	0.0018676	0.0032683
4	1	4	15	1	0.0037352	0.0070035
5	2	1	15	0.25	0.009338	0.016341
6	2	2	15	0.5	0.018676	0.035017
7	2	4	15	1	0.037352	0.072369
8	2	8	15	2	0.074704	0.14707
9	3	2	15	0.5	0.18676	0.33383
10	3	4	15	1	0.37352	0.70735
11	3	8	15	2	0.74704	1.4544
12	3	16	15	4	1.4941	2.9485
13	4	4	15	1	3.7234	6.6719
14	4	10	15	2.5	9.3085	15.98
15	4	20	15	5	18.617	34.597
16	4	40	362.25	241.5	899.2	933.8
Total time = 587.3 minutes (9 hours, 47 minutes, 15 seconds)						

Recipe

To make Solution 4 take 250 ml with concentration 3.7352 mg/ml and add 0.7919 ml pure water

Conclusion

- Platinum chemotherapy allergy is common; 46% ≥7 infusions of CA.
- Skin testing should ideally occur between 6/52 and 6/12 of the reaction.
- CA/OX are cross-reactive. CI allergy/cross-reactivity more rare.
- Drug desensitisation takes 4-12 hours, is temporary, and can be used to prevent immediate allergic and low-risk T-cell mediated reactions.
- Desensitisation of IgE-mediated allergy likely due to activation of SHIP-1 and prevention of downstream calcium influx.
- If no protocol exists, BSACI desensitisation protocol calculator is available.

References

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Feedback