Allergia a chemioterapici e farmaci biologici: dalla diagnosi alla desensibilizzazione

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Ipersensibilità a chemioterapici

- Nonostante l'avvento di nuove terapie biologiche, i farmaci chemioterapici **sono tuttora largamente utilizzati**

- Negli **USA** l'anafilassi da chemioterapici costituisce la **terza causa** di morte per anafilassi.

- L'allergia ai chemioterapici costituisce un **problema difficilmente aggirabile** a differenza di altre forme di allergia a farmaco

Classificazione dei chemioterapici

TABLE 1 Main characteristics of the most used CHT agents utilized in clinical practice

Drug category	Common generic drugs	Main clinical indications	Type of HSRs	Immunopathogenetic mechanisms of HSRs
Alkylating agents	Cyclophospamide Ifosfamide Melphalan Busulfan Dacarbazine Thiotepa Carmustine	Leukemia, Lymphomas, Multiple Myeloma, Breast cancer, bladder cancer	Rare, usually mild. Severe cases in very few patients	Not known
Anthracyclines and other antitumor antibiotics	Doxorubicin Epirubicin Bleomycin	Sarcomas, Breast, bladder, lung, thyroid cancer	Rare, namely dermatological effects	Not known
Antimetabolites	5-Fluorouracil Capecitabine Gemcitabine Fludarabine Methotrexate	Gastrointestinal, pancreatic, lung, head and neck cancer, lymphomas, leukemia	Rare, namely dermatological effects	Not Known
Bacterial Enzyme	Asparaginase	Acute Lymphoblastic leukemia	Incidence 6–40%, severe reactions in <10%	IgE and IgG specific antibodies involved
Cytoskeletal disruptors (taxanes)	Paclitaxel Docetaxel Nab-paclitaxel Cabazitaxel	Breast, ovarian, pancreas, lung, prostate, gastric, head and neck cancer	Usually after the first or second dose. Frequently back or pelvis pain.	Direct mastcell or complement activation. In some cases specific IgE are involved
Epipodophyllotoxins	Etoposide, teniposide	Lung cancer, lymphomas	Up to 40% of patients treated, usually mild	Direct mastcell or complement activation
Platinum-based agents	Carboplatin Cisplatin Oxaliplatin	Lung, ovarian, gastrointestinal, genitourinary cancer	Up to 40% for carbo after at least 7 doses. Severe in <2%	IgE-mediated, especially in most severe cases. Direct mastcell activation in other cases
Topoisomerase inhibitors	Irinotecan Topotecan	Lung, ovarian, colorectal cancer	Only adenoctal cases	Not known
Vinca Alkaloids	Vincristine Vinblastine	Lymphomas, lung, testicle cancer	Only adenoctal cases	Not known

Pagani M, Bavbek S, Alvarez-Cuesta E, et al. Hypersensitivity reactions to chemotherapy: an EAACI Position Paper. Allergy. 2022; 77: 388–403. https://doi.org/10.1111/all.15113

Epidemiologia

Sali di platino
-Carboplatino: 9-27% dei pazienti trattati con questo farmaco, incidenza che cresce sino al 46% nei pazienti sottoposti ad almeno 7 infusioni
-Oxaliplatino: 15% (range 1–25%) dei casi, 1% dei pazienti sperimenta gravi reazioni ritardate
-Cisplatino: 5-10% dei pazienti trattati

Taxani
-30% dei pazienti trattati
- l'incidenza si riduce a meno del 5% se si eseguono premedicazioni a base di steroidi e antistaminici

Asparaginasi → 6%- 43% dei casi, incidenza in aumento dopo la IV somministrazione

Epipodofillotossine (etoposide e teniposide) → 6.5% - 41%. La maggior parte non sono severe (>90%).

Sali di platino

Indicazioni: tumori del pancreas, ovarici, tratto GI, mammari, polmonari, rettali

Numerosi **effetti avversi**:
- nefrotossicità, neurotossicità e ototossicità

Patogenesi delle reazioni da **ipersensibilità**:
- **IgE** mediata e **non IgE** mediata

- I Sali di platino si legano alla **sieroalbumina umana** causando la formazione di apteni ad elevata stabilità che possono essere riconosciuti da cellule presentanti l'antigene

- Esiste una cross-reattività elevata tra farmaci della stessa classe, il **60-70%** dei pazienti sviluppa **reazioni multiple**

Sali di platino - fattori di rischio per ipersensibilità

- Generalmente insorgono dopo multiple somministrazioni → dopo **≥6** infusioni o **≥12mesi** di terapia
- **BRCA** 1-2 mutati aumentano il rischio
- Sesso **femminile**
- Carboplatino >>; cisplatino <

Taxani

- Utilizzo in K mammella, polmone, ovaio, prostata, distretto testa-collo, sarcoma etc.
- 95% delle reazioni si verifica durante **la I e la II** somministrazione
- **IgE-mediate** (20%) - anche alla I somministrazione per la presenza di taxani nei polli di *Taxus baccata* e nocciolo - e in parte reazioni legate all'attivazione del complemento diretta da parte di agenti emulsionanti(80%)
- Paclitaxel contiene polyoxyethylated castor oil (**Cremophor EL®**), docetaxel e cabazitaxel contengono polisorbato 80.
- *Paclitaxel albumin-bound nanoparticles (**Nab- paclitaxel**)* non contiene Cremophor EL ®.
- Pazienti con ST negativi e reazioni immediate lievi o non immediate hanno una probabilità più elevata di poter nuovamente tollerare il farmaco
- Cross reattività docetaxel – paclitaxel elevate in K mammella e ovarico

Caratteristiche delle reazioni, fattori di rischio

	Taxanes	Platinum compounds	Asparaginase
Presence of atopy	No	No	No
History of HSR to other drugs	Yes	Yes	No
Age	<70 years	<60 years	No
Gender	No	Female	No
Type of cancer	Not known	Not known	Not Known
Most involved drugs	Paclitaxel, Docetaxel	Carboplatin, oxaliplatin	*E. coli*-asparaginase preparation
Increased severity in previous reactions	Yes	Yes	Yes
Previous history of HSR to individual drugs	No	No	No

TABLE 2 Risk factors for developing HSRs with CTH drugs

Skin and mucosa	Warmth, flushing, itching, urticaria, angioedema
Head and Neck	Ocular itching, hyperemia, tearing, periorbital edema, Nasal itching, rhinorrhea, nasal congestion, sneezing Itching or tingling of lips, tongue, oral mucosa, metallic taste, angioedema of lips, tongue, uvula Sense of swelling in the throat, change in voice, hoarseness, difficulty in swallowing, stridor
Respiratory	Dyspnea, chest tightness, cough, wheezing, cyanosis
Cardiovascular	Faintness/dizziness, palpitation, syncope/loss of consciousness, tunnel vision, hypotension, cardiac arrest
Gastrointestinal	Nausea, vomiting, abdominal cramp/pain, diarrhea
Gynecological	Vaginal itching, uterin cramp/bleeding, incontinence
Neurological	Anxiety, sense of impending doom, altered mental status, seizures
Others	Back and chest pain

TABLE 3 Symptoms of immediate reactions to chemotherapeutic drugs

Pagani M, Bavbek S, Alvarez-Cuesta E, et al. Hypersensitivity reactions to chemotherapy: an EAACI Position Paper. Allergy. 2022; 77: 388–403. https://doi.org/10.1111/all.15113

Test cutanei

- A conferma delle reazioni **immuno-mediate** (vs reazioni da rilascio citochinico)
- Valutare **la cross-reattività** in caso di indicazione ad alternative terapeutiche appartenenti alla stessa classe farmacologica
- Lettura immediata (**2-3 settimane**) e ritardata

TABLE 4 Non-irritating concentrations of ST for chemotherapy

Drug	Prick test dilutions (mg/ml)	Intradermal test dilutions (mg/ml)
Paclitaxel	1/10 1 (6)	1/1000 (0.001 [0.006]) 1/100 (0.001 [0.006]) 1/10 (0.6) (ref. 32)
Docetaxel	1/1 4 (1)	1/100 (0.04 [0.01]) 1/10 0.4 ([0.1])
Carboplatin	1/1 (10)	1/100 (0.1) 1/10 (1)
Cisplatin	1/1 (10)	1/100 (0.01) 1/10 (0.1) 1/1 (1)
Oxaliplatin	1/1 (5)	1/100 (0.05) 1/10 (0.5) 1/1 (5) -some authors have found false positives (ref. 32)-
L-Asparaginase	A drop of reconstitute 5000 KU	0.01 ml of reconstitute 5000 KU
Methotrexate	1/1 (10)	1/100 (0,1) 1/10 (1) 1/1 (10)
Procarbazine	1/1 (5)	1/100 (0.05)
Gemcitabine	1/1 (38)	1/1000 (0.0038) 1/100 (0.038) 1/10 & 1/1 (ref. 32)

Pagani M, Bavbek S, Alvarez-Cuesta E, et al. Hypersensitivity reactions to chemotherapy: an EAACI Position Paper. Allergy. 2022; 77: 388–403. https://doi.org/10.1111/all.15113

Stratificazione del rischio

TABLE I. Local adaptation of a multifactorial risk stratification tool

Stratification of Risk Into Low-, Medium-, and High-Risk Patients as per the ICO-HUB Scale
High-risk criteria
Severe initial reaction (grade 3 Brown or grade 3–4 RCUH)
Positive skin prick testing
Positive intradermal test + major risk factor regardless of severity of initial reaction
REMA score ≥ 2
Medium-risk criteria
Mild initial reactions (grade 1 Brown and RCUH) + major risk factor
Negative skin testing + moderate initial reaction (grade 2 Brown and RCUH)
Mild or moderate initial reactions (grade 1 or 2) + positive/equivocal intradermal testing + no major risk factors
Low-risk criteria
Mild initial reactions (grade 1 Brown and RCUH) + negative skin test + no major risk factors
Major risk factors
The patient is not well enough to withstand anaphylaxis or has comorbidities that might trigger a situation beyond medical control
FEV_1 < 1 L or < 80%
Initial reaction grade 4 RCUH (shock)
Significantly raised tryptase during the reaction (compared with baseline)
Age > 75 y
Unavoidable intake of β-blockers or ACEIs
Cognitive impairment, sensory impairment, language barrier, or difficulty identifying and communicating a reaction
Skin testing performed before 4 wk (theoretical risk of false negatives)
Criteria for immediate reactions
Reactions with features of type I Gell and Coombs reactions* (or CRR) occurring during the drug infusion or within 1–6 h after the last drug administration
Criteria for nonimmediate reactions
Reactions with features of type II–IV Gell and Coombs reactions* (or CRR) at any time as from 1 h after from the initial drug administration

ACEI, Angiotensin-converting enzyme inhibitor; *CRR,* cytokine release reaction; *FEV_1,* forced expiratory volume in 1 second; *HUB,* Bellvitge University Hospital, Barcelona, Spain; *ICO,* Catalan Institute of Oncology, Barcelona, Spain.
Adapted from Vázquez-Revuelta P, Lleonart-Bellfill R, Molina-Mata K, Muñoz-Sánchez C, Rey-Salido M, Madrigal-Burgaleta R. A pilot experience using a 1-bag intravenous rapid desensitization protocol for chemotherapy and biologics in a cohort of patients with access to a delabeling pathway. J Investig Allergol Clin

- Indicazioni a **RDD (rapid drug desensitization):**

→ Esito dei test cutanei (da eseguirsi a 2-6 settimane); Del BAT e elevazione triptasi in corso di reazione

→ Severità della reazione: reazioni IgE mediate di grado moderato-severo

→ Nessuna indicazione per malattia da siero

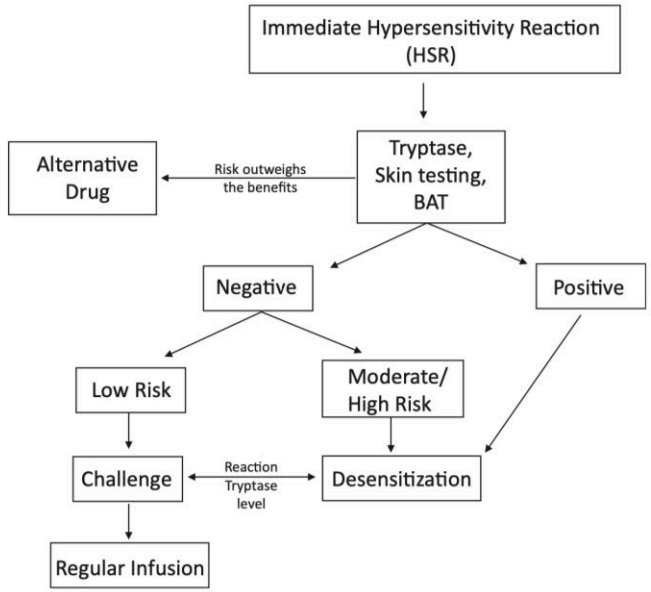


FIGURE 1. Brigham and Women's Hospital clinical risk stratification tool for the management of hypersensitivity reactions to chemotherapeutic agents and biologics. *BAT,* Basophil activation test.

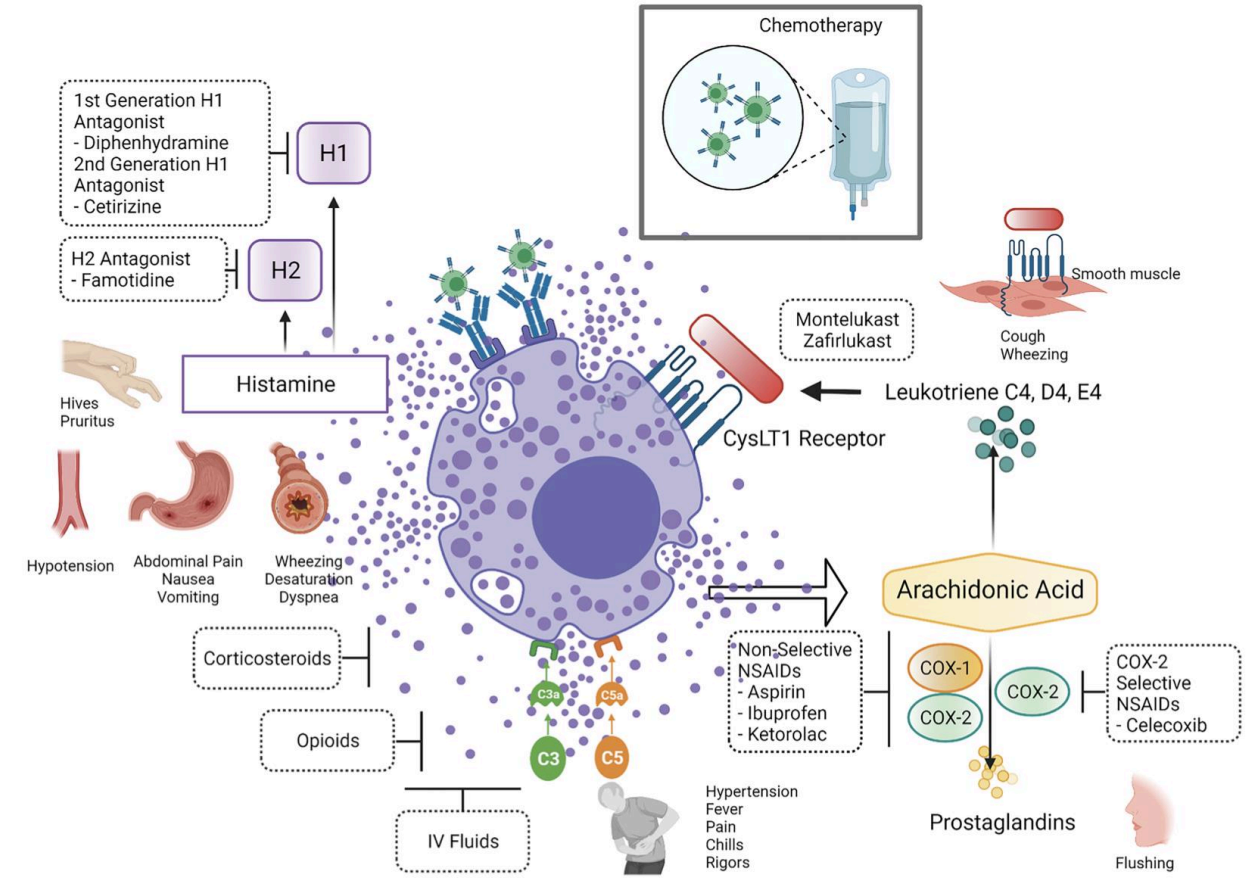
Protocolli di premedicazione

- Con la premedicazione, HSR a paclitaxel si verificano nel 10–20% dei pazienti, con reazioni severe solo nel 2–4% dei pz

- La **riduzione della velocità di infusione**, aumentando l'idratazione ev con l'aggiunta di **meperidina** può essere utilizzata per ridurre l'insorgenza di **brivido** legata al rilascio citochinico

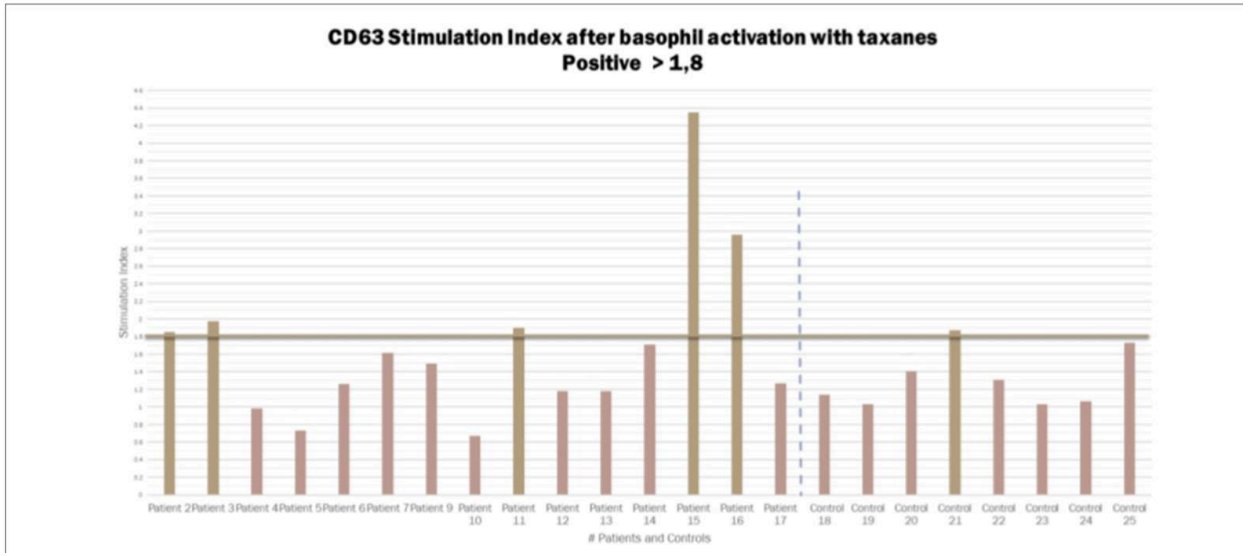
- Allo scopo di ridurre il flushing in corso di reazione, alcuni protocolli prevedono l'aggiunta di **ASA 325 mg**

- Gli **antileucotrienici** si utilizzano allo scopo di ridurre il rischio di sintomi **respiratori** durante l'infusione



Ruolo del BAT

- Utile nella diagnostica delle reazioni da ipersensibilità a taxani
- In questo studio è stato analizzato in un gruppo di 15 pazienti a confronto con 8 controlli positivi. I pz avevano storia di reazioni **gravi** e coinvolgimento **cutaneo**



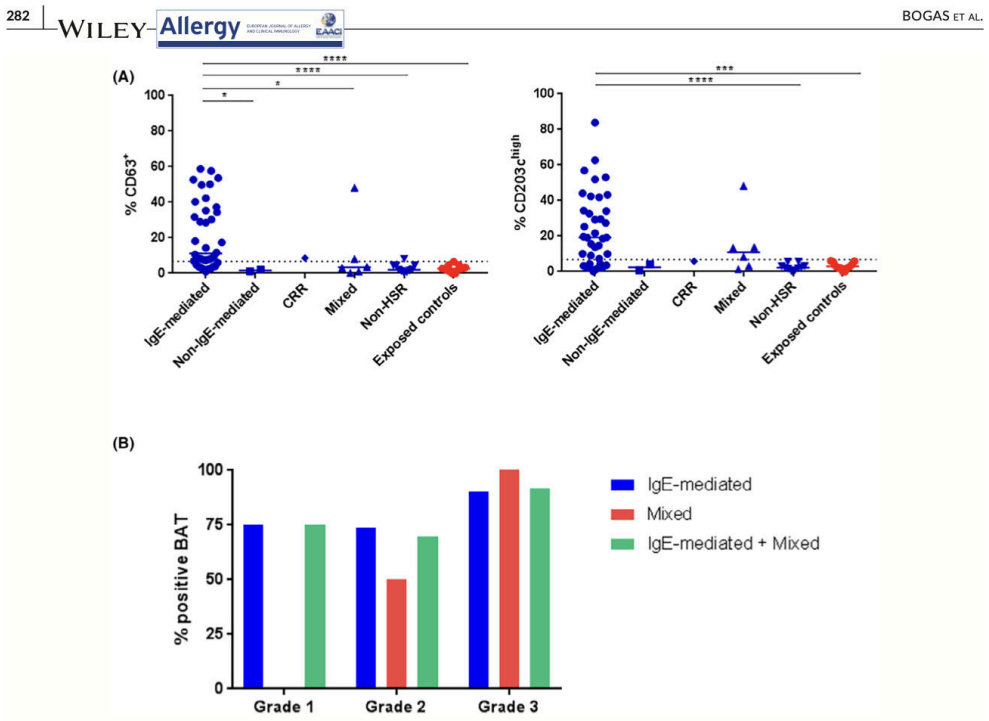


FIGURE 3 (A) BAT results according to the endotype for PSs using %CD63 and %CD203c. *$p < .05$. ***$p < .001$. ****$p < .0001$. (B) percentage of patients giving positive results in BAT according to the severity of the reaction.

Reazioni in corso di RDD

Reazioni in corso di RDD (*breakthrough reactions*) si verificano nel 12% -40%dei casi, la maggior parte indotte dai **Sali di platino**.

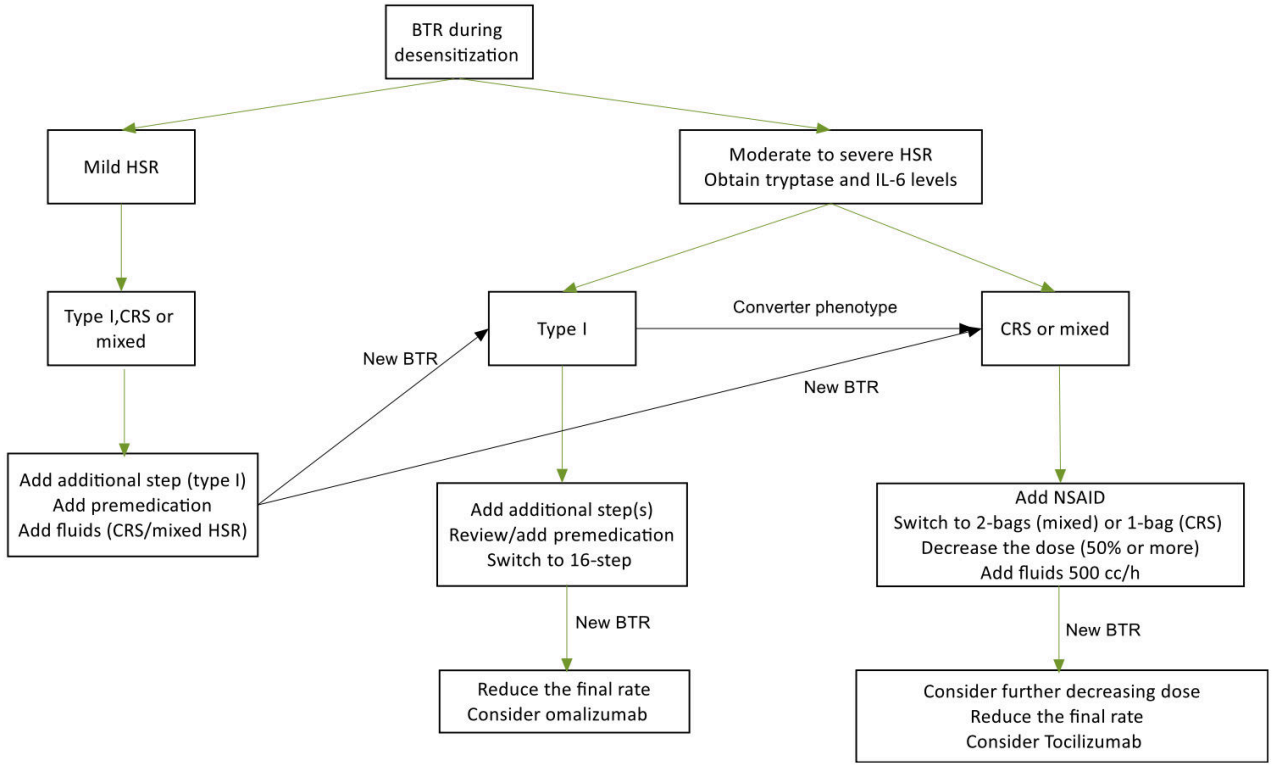
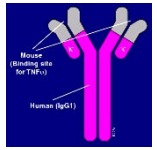


Figure 2. Algorithm with different strategies to reduce the risk of breakthrough reactions during desensitization procedures. These strategies are based on the severity of the reaction, phenotype, and available biomarkers. BTR, breakthrough reaction; CRS, cytokine release syndrome; NSAID, nonsteroidal anti-inflammatory drug.

Ipersensibilità a biologici

→CITOCHINE (ES: IFN-a, IFN-b, IL-2)



→ANTICORPI

- **chimerici** (mAb umani al 75%) ximab es: infliximab
- **umanizzati** (mAb umani al 95%) zumab es: omalizumab
- **umani** mumab (mAb umani al 100%) es: adalimumab

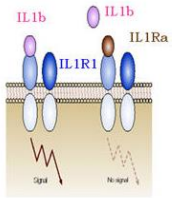
1. ***ANTI CITOCHINE*** (es: anti-IL5, anti-TNF)
2. ***AC BLOCCANTI MOLECOLE SULLA CELLULA*** (es: Ac anti- IL5R benralizumab)
3. ***AC IN GRADO DI IMPOVERIRE/INATTIVARE ALCUNE CELLULE*** (es: ac anti CD20) oppure diretti contro Ag tumorali
4. ***CHECKPOINT INHIBITORS*** (immunoterapia adottiva: es: antiCTLA-4, anti-PD1)

→PROTEINE DI FUSIONE (es: anakinra **ANTAGONISTA RECETTORE IL-1β)**

Table 3. Types of biologicals (examples)

Cytokines
IFN-α, IFN-β, IL-2, etc.
Antibodies
To soluble proteins like cytokines: anti-TNF-α (infliximab or adalimumab), anti-IL-2 (daclizumab)
To cell surface molecules: anti-CD20 (rituximab); anti-IL-2 receptor (basiliximab), anti-LFA-1 (efalizumab)
To IgE (omalizumab)
To tumour antigens (e.g. EGFR, cetuximab, anti-HER2, trastuzumab)
Fusion proteins (soluble receptors for cytokines or soluble cellular ligands)
TNF-αRII (etanercept), a soluble TNF-α receptor
CTLA4-Ig (abatacept) blocking CD28–CD80/CD86 interaction
IL-1 receptor antagonist (anakinra)*

*Not a fusion protein, but acting in a similar way.
EGFR, epidermal growth factor receptor; IFN, interferon; IL, interleukin; TNF, tumour necrosis factor; IgE, immunoglobulin E.



Ipersensibilità a biologici
Epidemiologia

Rituximab →5-10%

Infliximab→ 2-3%

Cetuximab→ 3-22%

Trastuzumab→ 0.6-5%

Dipendente da vari fattori:

1) Grado di umanizzazione
2) Pattern di glicosilazione
3) Intervallo tra le dosi
4) Caratteristiche del paziente
5) Eccipienti

Cetuximab → ipersensibilità IgE mediata anche alla I somministrazione, Sensibilizzazione possibile tramite alpha gal

NB:
Le reazioni da ipersensibilità possono essere legate agli eccipienti dei farmaci (es. polisorbato 20 in Omalizumab e polisorbato 80 in darbopoetina e EPO)

Ipersensibilità a biologici

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

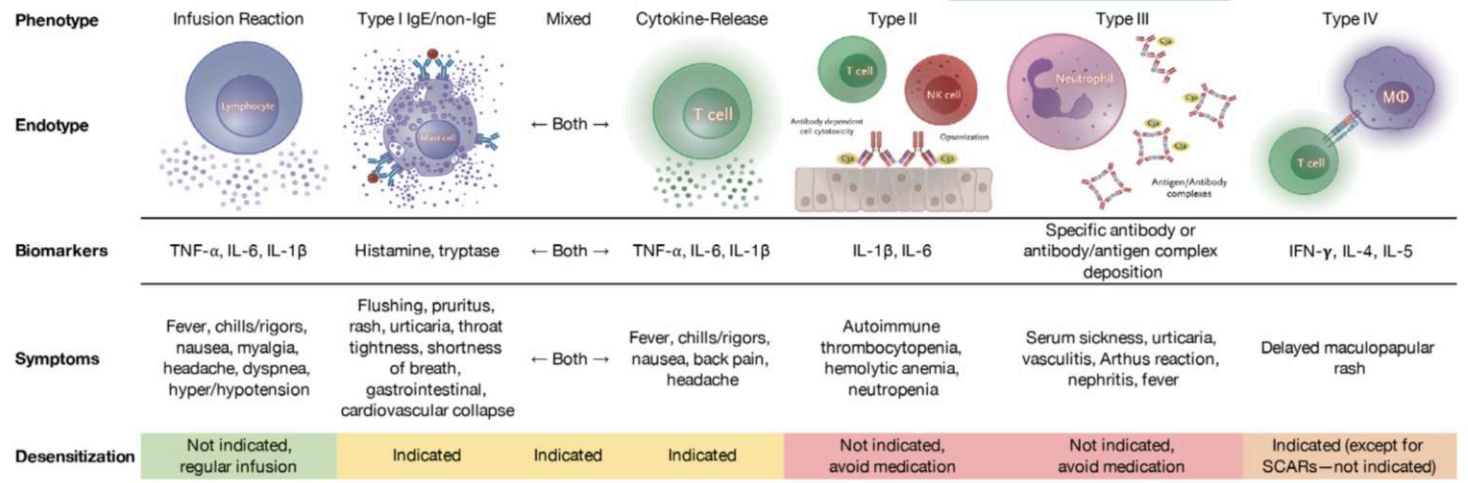


FIGURE 1 Classification of hypersensitivity reactions to biologicals. Type IV reactions are indicated except for severe cutaneous adverse reactions (SCARs), which necessitate drug avoidance altogether.

Presentazione clinica:

1) IRR→ lievi moderate, simili a tipo I ma migliorano alla riesposizione

2) CRR→febbre/brivido, nausea, dolore, cefalea e rigidità

3) Tipo I (IgE/non IgE)

4) Miste

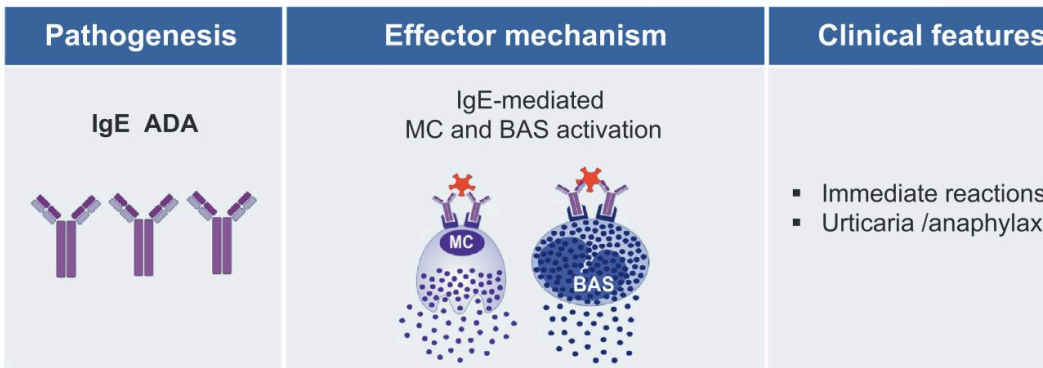
5) Tipo III (serum sickness)→ febbre, malessere, artralgie, porpora, infiltrazione polmonare, splenomegalia

6) Injection site reactions

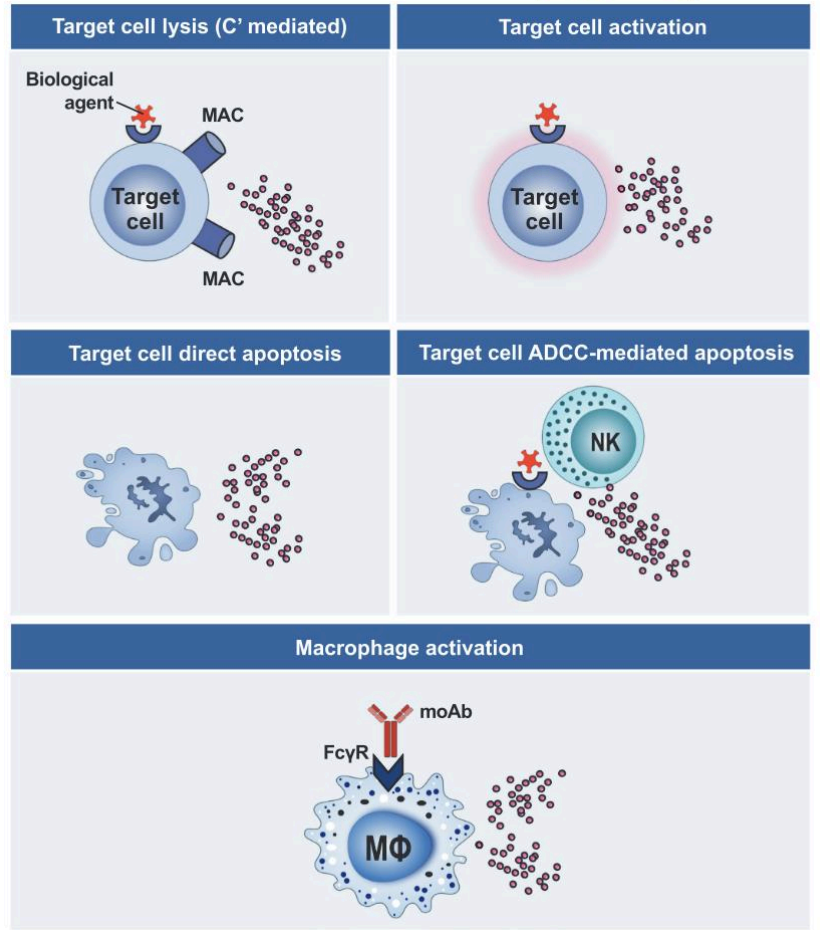
Ipersensibilità a biologici

ADA mediated reactions

Pathogenesis	Effector mechanism	Clinical features
IgE ADA	IgE-mediated MC and BAS activation	▪ Immediate reactions ▪ Urticaria /anaphylaxis
IgG ADA	▪ C' activation ▪ Release of: C3a and C5a	▪ Immediate reactions ▪ Urticaria /anaphylaxis
IgG ADA	IgG-mediated BAS activation	▪ Immediate reactions ▪ Urticaria /anaphylaxis



Non-ADA mediated reactions



Ipersensibilità a biologici

Test in vivo

Authors (year), Ref (.)	Drug concentration	Dilution for Prick test	Dilution for IDT	No. cases
Infliximab				
Vultaggio (2010)[38]	10 mg/ml	1:1000–1:1	1:10000–1:10	11
Matucci (2013)[30]	10 mg/ml	1:1000–1:1	1:1000–1:1	23
Freling (2015)[77]	2 mg/ml	1:10–1:1	1:100–1:1	24
Brennan (2009)[50]	10 mg /ml	1:1	1:100–1:10	6
Bavbek (2016)[18]	10 mg/ml	1:1	1:1000–1:10	1
Madrigal-Burgaleta (2019)[17]	10 mg/ml	1:1	1:10-1:1	10
Adalimumab				
Benucci (2008)[74]	50 mg/ml	1:1	1:10–1:1	2
Bavbek (2015)[75]	40 mg/ml	1:1000–1:1	1:1000–1:1	5
Madrigal-Burgaleta (2019)[17]	40 mg/ml	1:1	1:10-1:1	4
Etanercept				
Bavbek (2015)[75]	50 mg/ml	1:1	1:1000–1:10	7
de la Varga Martinez[76]	25 mg/ml	1:1	1:100–1:10	2
Benucci (2008)[74]	25 mg/ml	1:1	1:5–1:250	2
Madrigal-Burgaleta (2019)[17]	25 mg/ml	1:1	1:10-1:1	1

Bavbek S, Pagani M, Alvarez-Cuesta E, et al. Hypersensitivity reactions to biologicals: An EAACI position paper. Allergy. 2022; 77: 39–54.

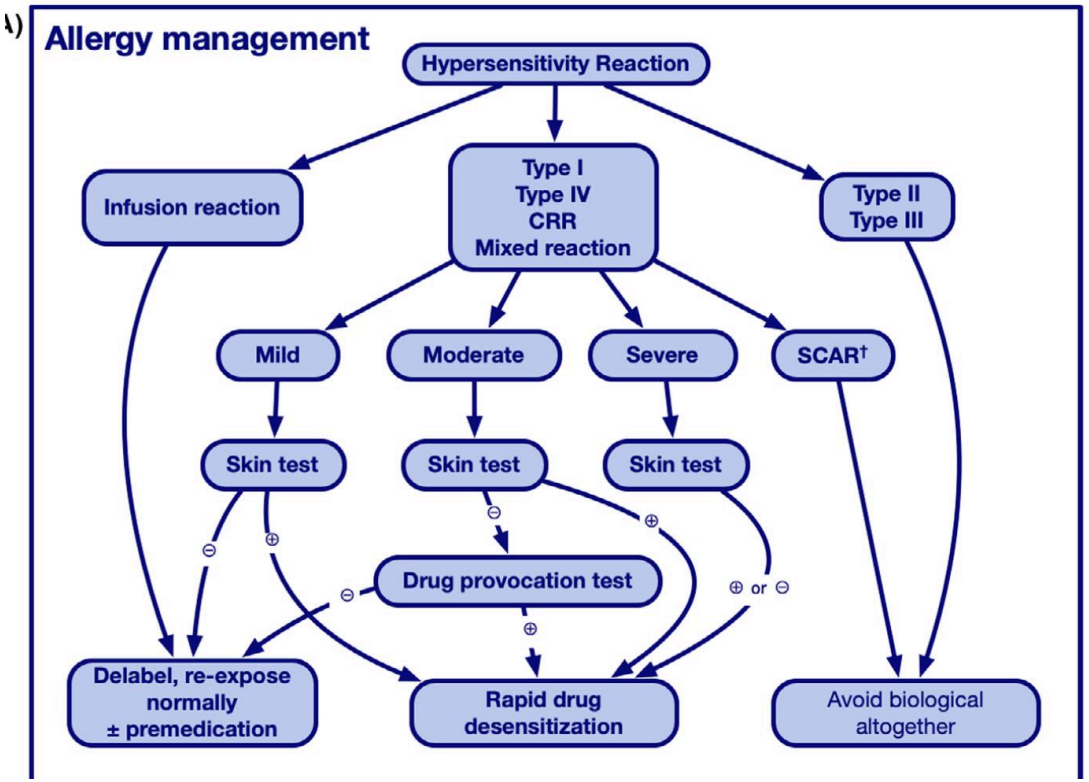
BIOLOGICS		
Bevacizumab	25 mg/ml	2.5 and 25 mg/ml
Brentuximab	5 mg/ml	0.5 and 5 mg/ml
Rituximab	10 mg/ml	1 and 10 mg/ml
Panitumumab	20 mg/ml	2 and 20 mg/ml
Pertuzumab	30 mg/ml	3 and 30mg/ml
Trastuzumab	21 mg/ml	2.1 and 21 mg/ml

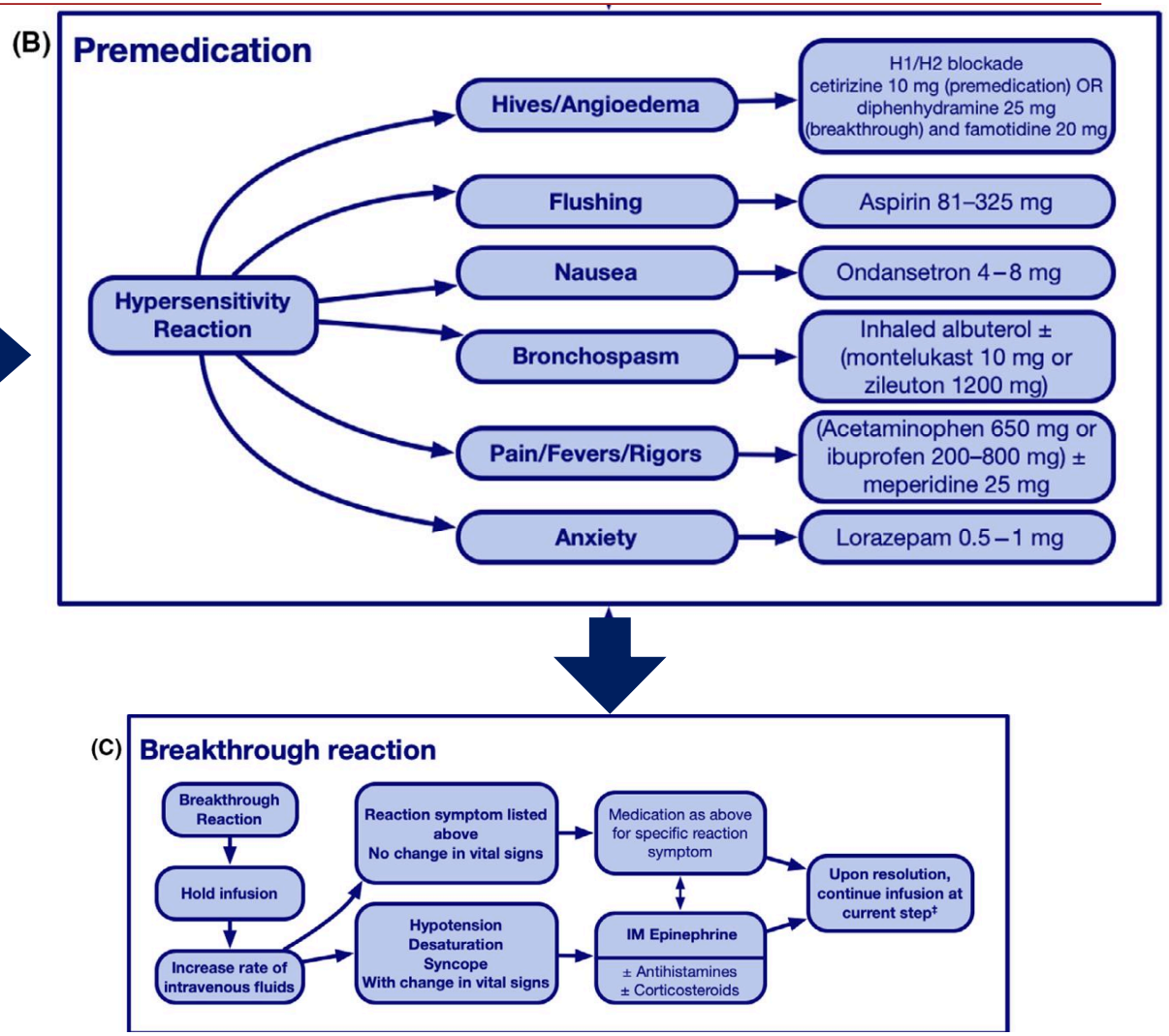
J Investig Allergol Clin Immunol 2023; Vol. 33(4): 289-291
doi: 10.18176/jiaci.0860

Test in vitro

Il dosaggio degli anticorpi ADA, viene effettuato mediante test ELISA e la presenza di IgE specifiche antifarmaco traminte ImmunoCAP è altamente associata alla positività ai test cutanei

Ipersensibilità a biologici





Yang, B.C. and Castells, M. (2025), Medical algorithm: Diagnosis and treatment of drug hypersensitivity reactions to biologicals, 2024 update. Allergy, 80: 1534-1539. https://doi-org.sanraffaele.idm.oclc.org/10.1111/all.16353

Ipersensibilità a biologici

3 bag desensitization

Name of medication:		***Bevacizumab***				
Target Dose (mg)				800		
Standard volume per bag (mL)				250		
Final rate of infusion (mL/h)				80		
Calculated target concentration (mg/mL)				3.2		
Standard time of infusion (minutes)				187.5		
					Total mg per bag	Amount of bag infused (mL)
Solution 1	250	mL of	0.032	mg/mL	8.000	9.25
Solution 2	250	mL of	0.320	mg/mL	80.000	18.75
Solution 3	250	mL of	3.175	mg/mL	793.704	250.00

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0160	0.0160
2	1	5.0	15	1.25	0.0400	0.0560
3	1	10.0	15	2.50	0.0800	0.1360
4	1	20.0	15	5.00	0.1600	0.2960
5	2	5.0	15	1.25	0.4000	0.6960
6	2	10.0	15	2.50	0.8000	1.4960
7	2	20.0	15	5.00	1.6000	3.0960
8	2	40.0	15	10.00	3.2000	6.2960
9	3	10.0	15	2.50	7.9370	14.2330
10	3	20.0	15	5.00	15.8741	30.1071
11	3	40.0	15	10.00	31.7482	61.8553
12	3	80.0	174.375	232.50	738.1447	800.0000
		Total time (minutes) =	339.375	= 5.66 h		

1 bag desensitization

TABLE II. Example of dosing for 130 mg of oxaliplatin diluted in 525 cc of volume (0.247 mg/mL)

Rate (mL/h)	Time (min)	Accumulated time (min)	Volume (mL)	Accumulated volume (mL)	Dose (mg)	Accumulated dose (mg)
5	15	15	1.25	1.25	0.3	0.3
10	15	30	2.5	3.75	0.68	0.98
25	15	45	6.25	10	1.54	2.52
50	15	60	12.5	22.5	3.08	5.6
75	15	75	18.75	41.25	4.63	10.23
100	15	90	25	66.25	6.17	16.4
150	15	105	37.5	103.75	9.26	25.66
200	15	120	50	153.75	12.35	38.01
250	89.16	209.16	371.5	525	91.76	129.77

4 bag desensitization

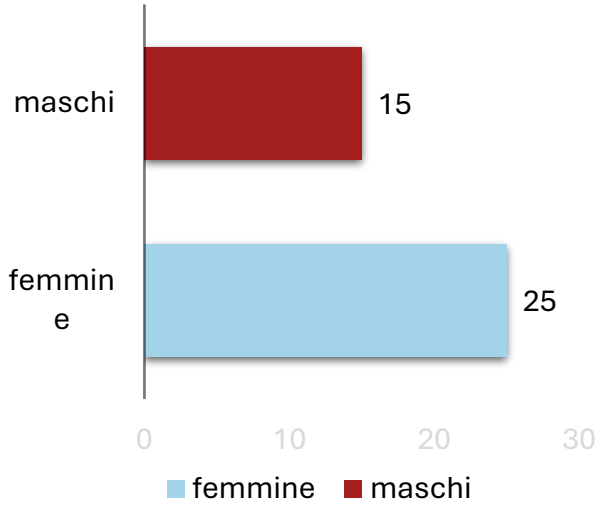
Name of medication:		***Gemcitabine***				
Target Dose (mg)				1122.0		
Standard volume per bag (ml)				250		
Final rate of infusion (ml/hr)				80		
Calculated final concentration (mg/ml)				4.488		
Standard time of infusion (minutes)				187.5		
					Total mg per bag	
Solution 1	250	ml of	0.002	mg/ml	0.561	
Solution 2	250	ml of	0.045	mg/ml	11.220	
Solution 3	250	ml of	0.449	mg/ml	112.200	
Solution 4	250	ml of	4.453	mg/ml	1113.143	

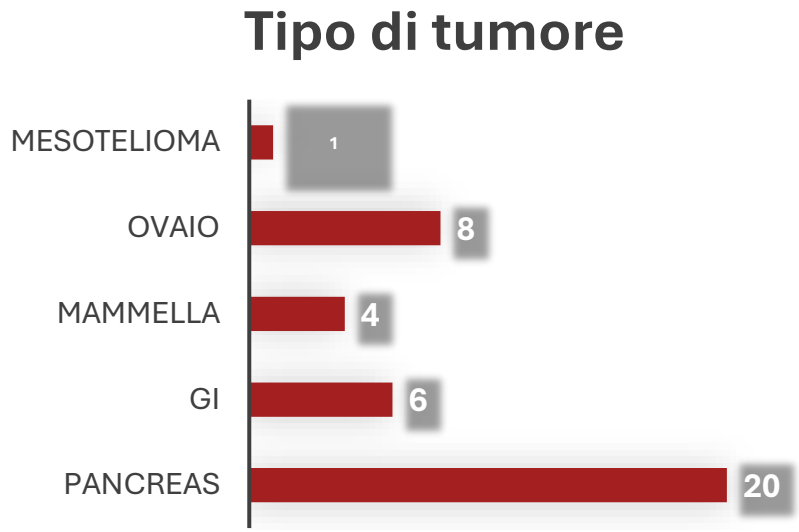
Step	Solution	Rate (ml/hr)	Time (min)	Volume infused per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.5	15	0.625	0.001	0.001
2	1	5	15	1.25	0.003	0.004
3	1	10	15	2.5	0.006	0.010
4	1	20	15	5	0.011	0.021
5	2	2.5	15	0.625	0.028	0.049
6	2	5	15	1.25	0.056	0.105
7	2	10	15	2.5	0.112	0.217
8	2	20	15	5	0.224	0.442
9	3	5	15	1.25	0.561	1.003
10	3	10	15	2.5	1.122	2.125
11	3	20	15	5	2.244	4.369
12	3	40	15	10	4.488	8.857
13	4	10	15	2.5	11.131	19.988
14	4	20	15	5	22.263	42.251
15	4	40	15	10	44.526	86.777
16	4	80	174.375	232.5	1035.223	1122.000
		Total time (minutes) =	399.375	= 6.66 hrs		

Sloane D, Govindarajulu U, Harrow-Mortelliti J, et al. Safety, Costs, and Efficacy of Rapid Drug Desensitizations to Chemotherapy and Monoclonal Antibodies. *J Allergy Clin Immunol Pract*. 2016;4(3):497-504. doi:10.1016/j.jaip.2015.12.019

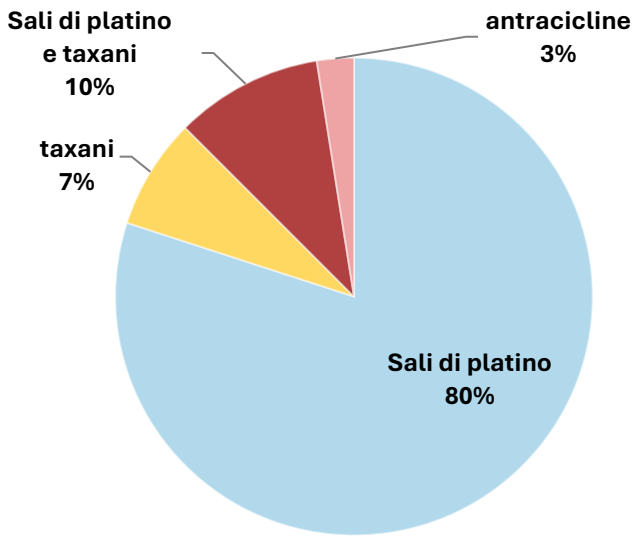
La nostra casistica

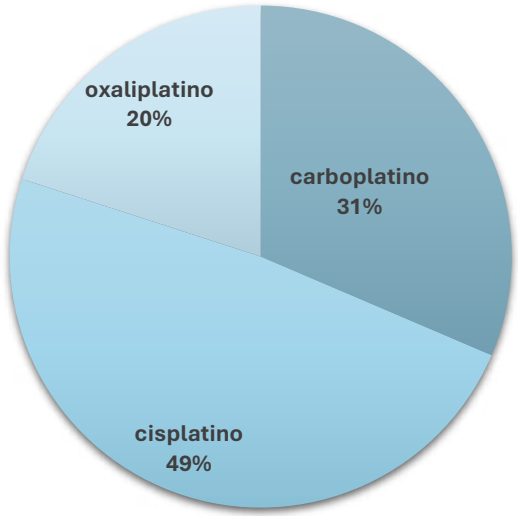
- Età mediana 62 (54;70)
- Pazienti afferenti alla nostra U.O. dal 01/2025 al 01/2026 all'interno del Cancer Center dell'ospedale San Raffaele

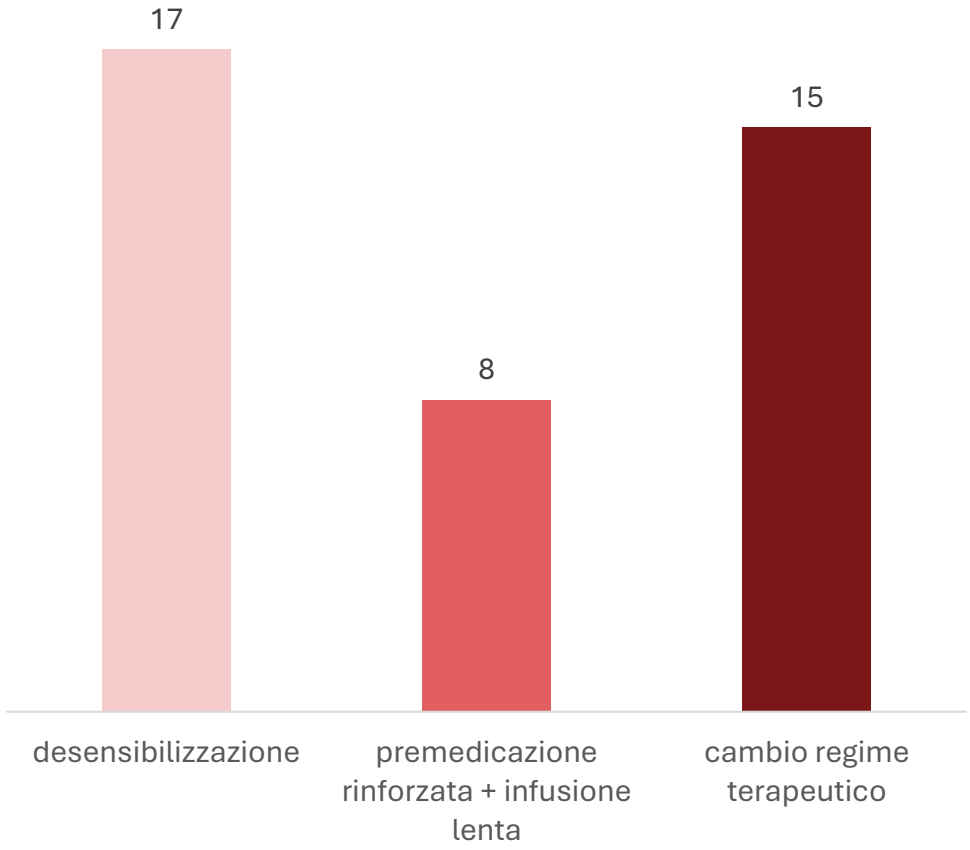




La nostra casistica

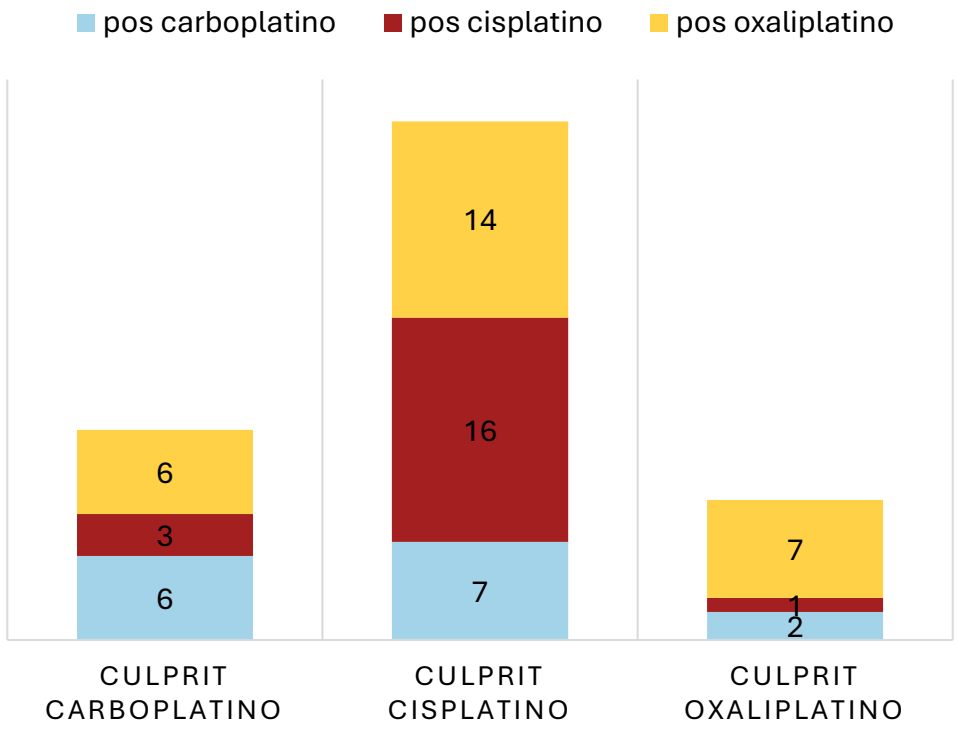


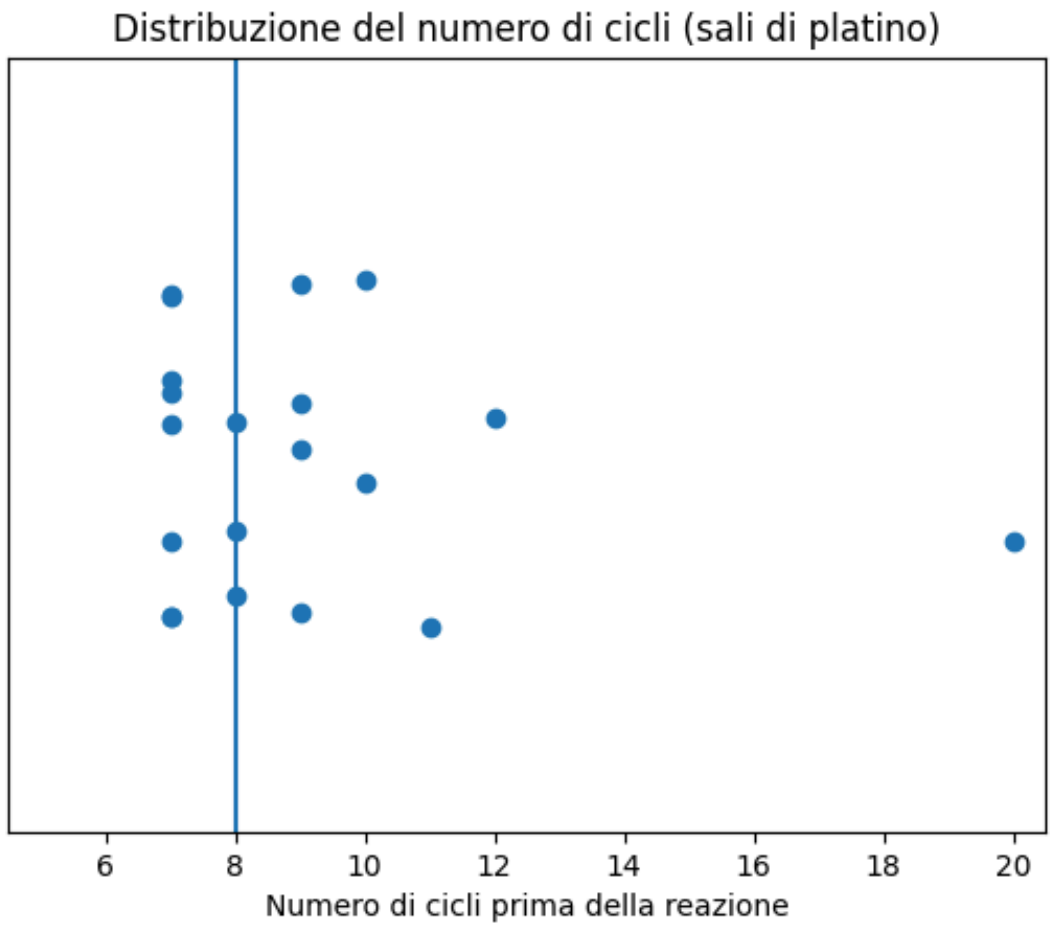




Tutti i pazienti sottoposti a desensibilizzazione o a premedicazione rinforzata hanno in seguito tollerato la terapia

La nostra casistica





Conclusioni

1. La gestione dell'ipersensibilità ai chemioterapici richiede un **approccio personalizzato e multidisciplinare**.

2. Test cutanei e RDD devono essere integrati nella valutazione clinica in base a **rischio, gravità e necessità terapeutica**.

3. La collaborazione con la farmacia ospedaliera è un **elemento chiave** per sicurezza ed efficacia del percorso.

Grazie per l’attenzione