**MATERIAL SUPPLEMENTARY**

**Supplemental Table 1:** Non-irritating skin testing concentrations for chemotherapy and biologics used at the ICO-HUB Drug Desensitisation Centre

| Drug | Skin prick testing concentrations | Intradermal testing concentrations |
|---|---|---|
| **TAXANES** | | |
| Docetaxel | 10 mg/ml | 0.1 and 1 mg/ml |
| Paclitaxel | 6 mg/ml | 1 mg/ml |
| **PLATINS** | | |
| Carboplatin | 10 mg/ml | 1 and 5 mg/ml |
| Cisplatin | 1 mg/ml | 0.1 and 1 mg/ml |
| Oxaliplatin | 5 mg/ml | 0.5 and 1 mg/ml |
| **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 |
| **OTHERS** | | |
| Calcium folinate | 10 mg/ml | 1 and 10 mg/ml |
| Doxorubicin | Not done (vessicant) | Not done (vessicant) |
| Etoposide | 20 mg/ml | 2 and 20 mg/ml |
| Gemcitabine | 38 mg/ml | 0.0038 and 0.038 mg/ml |



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| | | |
|---|---|---|
| Irinotecan | 20 mg/ml | 2 and 20 mg/ml |
| Pemetrexed | 25 mg/ml | 0.25 and 2.5 mg/ml |
| 5-fluorouracil | 50 mg/ml | 5 and 50 mg/ml |

**Legend:** ICO, Catalan Institute of Oncology. HUB, Bellvitge University Hospital.

**Further considerations:**

These concentrations were tested in at least ten non-reactive patients to prove them nonirritant.

Skin testing solutions for all these drugs were prepared by the Pharmacy Service Cytotoxic Unit. For the skin prick test, a drop of the drug at the maximal concentration was applied to the volar surface of the forearm by the use of a skin prick test lancet. If prick test were negative, for intradermal injections, 0.03 ml of the drug to reach a 3 mm bleb (first at minimal concentration, and, if negative, maximal concentration) was injected. A positive reaction for skin prick testing was defined as a weal with a diameter at least 3 mm larger than that produced by a negative control (NaCl 0.9%). Histamine (10 mg/ml) was used as a positive control.

A positive reaction for intradermal testing was defined as a growth in the initial bleb of over 3 mm with erythema and itch. Equivocal reactions included those in which the growth of over 3 mm was not in line with a typical positive intradermal test (e.g., isolated growth with limited erythema and pain or irritation instead of itch).

Whenever possible, skin tests were performed at least two weeks after initial reaction, to avoid false-negative results. However, when the chemotherapy scheme required the next administration to be given before two weeks, we went ahead with skin testing before the two weeks limit, as we prioritized respecting chemotherapy scheme timings. As explained in table 1, we considered that patients who underwent skin testing before a four-week time after their reaction could be at risk of a false negative skin testing result, and this should be a factor to consider in the risk assessment.



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Supplemental table 2. Example of the standard flexible ICO-HUB single-bag rapid drug desensitization protocol for a total dose of 200 mg of oxaliplatin meant to be administered in a volume of 500 ml over two hours.

| Total dose | 200 mg | | Solution concentration | | Total dose in the bag (mg) | | Drug |
|---|---|---|---|---|---|---|---|
| Solution A | 500 ml | | 0.4 mg/ml | | 200 | | Oxaliplatin |
| Step | Solution | Rate (ml/h) | Administered volume (ml) | Time (min) | Administered dose (mg) | **Fold increase per step (mg/min)** | Cumulative dose infused (mg) |
| 1 | A | 1 | 0.25 | 15 | 0.1 | NA | 0.1 |
| 2 | A | 2 | 0.5 | 15 | 0.2 | x2 | 0.3 |
| 3 | A | 4 | 1 | 15 | 0.4 | x2 | 0.7 |
| 4 | A | 8 | 2 | 15 | 0.8 | x2 | 1.5 |
| 5 | A | 16 | 4 | 15 | 1.6 | x2 | 3.1 |
| 6 | A | 32 | 8 | 15 | 3.2 | x2 | 6.3 |
| 7 | A | 48 | 12 | 15 | 4.8 | x1.5 | 11.1 |
| 8 | A | 72 | 18 | 15 | 7.2 | x1.5 | 18.3 |
| 9 | A | 108 | 27 | 15 | 10.8 | x1.5 | 29.1 |
| 10 | A | 162 | 40.5 | 15 | 16.2 | x1.5 | 45.3 |
| 11 | A | 250 | 386.75 | 1 h 33 min | 154.7 | x1.5 | 200 |
| Total infusion time: 243 min (4 hours and 3 minutes) | | | | | | | |
| **Safety considerations:** As per international guidance, this RDD protocol should only be used by expert allergists with access to allergy-dedicated spaces prepared and staffed for this allergy-specific high-risk and high-complexity procedure. | | | | | | | |
| **Premedication:** This is a premedication-sparing one-bag protocol. However, premedication should comply with the manufacturer's instructions and institutional protocols for standard infusion for each specific drug. We do not recommend additional systematic premedication (e.g., steroids or antihistamines) to prevent breakthrough reactions, especially for the first procedure. However, tailored premedication can be added depending on a personalized case-to-case approach (in our centre, primarily in patients that have experienced previous breakthrough reactions during RDD). | | | | | | | |
| **Adjustments to the volume of the bags:** The standard volume in the solution bags for the ICO/Bellvitge protocol is 500 ml, as long as this is considered an option in the manufacturer's instructions. In some cases, bag volume might need adjustment depending on the manufacturer's instructions or product information. | | | | | | | |
| **Simultaneous diluting fluids**: A 500 ml saline 0.9% bag (or glucose 5% for platins) is infused simultaneously via the same line (dual lumen). The flow rate for the fluids is programmed following the same protocol as the drug. This prevents human mistakes (which could come from having different flow rates for the drug and for the fluids) and ensures that the dilution of the culprit drug is consistent throughout the process. | | | | | | | |
| **Adjustments to the fold increase between steps:** The fold increase is x2 until step 6, and it changes to x1.5 from then on. Different fold increases between steps could be used when personalizing protocols (e.g., in reactive patients in whom a more cautious increase might be added in reactive steps, or in cases when protocol calculation is made easier by making a minor adjustment). Fold increase between steps should be within recommendations by rapid drug desensitization guidelines. | | | | | | | |
| **Adjustments to final infusion rate:** Step 11 may be adapted to the desired final infusion rate. The final infusion rate can be adapted to mimic the standard regimes indicated by the referring oncologist or for personalization in reactive patients (e.g., a slower final infusion rate). Moreover, additional steps may be added to reach higher infusion rates while maintaining a maximum dose increasing between 1.25-fold to 2.5-fold with each step. | | | | | | | |
| **Infusion pumps:** Precision infusion pumps should be used to accurately follow the protocol, which features very small volumes in most steps. These pumps should have automatic multi-step infusion options to avoid human errors associated with manually changing infusion rates every 15 minutes. | | | | | | | |

**Legend:** NA, not applicable; RDD, rapid drug desensitization; ICO, Catalan Institute of Oncology, Barcelona, Spain; HUB, Bellvitge University Hospital, Barcelona, Spain



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