Pilot Experience Using Drug Provocation Testing for the Study of Hypersensitivity to Chemotherapy and Biological Agents

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Delabeling is becoming paramount in drug allergy pathways [1]. However, data on delabeling patients with reactions to chemotherapy and biologics is limited to a few specialized centers with specific populations [2-4]. A recent publication that focused on drug provocation testing (DPT) for delabeling patients who react to chemotherapy and biologics led us to reconsider our local pathways [5].

Our center has longstanding experience with rapid drug desensitization (RDD), a technique that enables patients to receive their treatment safely despite being allergic [6-7]. Receiving chemotherapy by means of RDD does not affect survival (ie, does not affect the efficacy of the drugs) and is cost-effective [8-9]. However, since RDD is needed for each administration of the drug, these resource-intensive procedures tend to accumulate, thus generating waiting lists. Therefore, delabeling patients with a favorable risk assessment seems reasonable and efficient.

Our main objective was to audit our pilot experience after implementing DPT in the pathways of our drug desensitization center (DDC), a multidisciplinary team with access to dedicated spaces that are fully integrated in Duran i Reynals Hospital, Barcelona, Spain, a dedicated oncology center that receives patients from the Catalan Institute of Oncology’s referral network. Our secondary objective was to monitor the activity of the DDC.

We performed a retrospective analysis of our database and included all the patients referred to the DDC between January 2018 and March 2019 (15 months). Ethics committee approval was obtained (PR165/20). Data were obtained from the clinical history, including skin testing (ST) and DPT results, as well as information on RDD. Only patients reacting to intravenous drugs within 48 hours of administration were included.

Initial reactions were classified as immediate (occurring during drug infusion or within 1 hour after completion of the infusion) and nonimmediate (>1 hour after completion of the infusion), and their severity was graded according to both the Brown classification and the Ramon y Cajal University Hospital (RCUH) classification [2,10]. Patients were then classified as low or high-risk patients, according to the RCUH recommendations [2].

ST, including skin prick testing (SPT) and intradermal testing (IDT), was performed according to the standard operating procedures of the European Academy of Allergy and Clinical Immunology [11], following the recommended concentrations and safety measures for chemotherapy as per RCUH [2,6].

Low-risk patients with a mild reaction and negative skin test result were offered DPT. Patients were empowered to make the final decision on DPT after a multidisciplinary decision-making process in which the oncologist confirmed the indication and the allergist conducted the risk assessment [2,12-13]. Concomitant drugs (eg, other chemotherapy or biological agents, leucovorin, antiemetics) that could be involved in the reaction were studied separately with ST and DPT to confirm tolerance, although these were not included in the analysis [2,14].

Patients with a negative DPT were delabeled and considered nonallergic. Patients with a positive ST and/or positive DPT result and/or a high-risk assessment were offered RDD [2,5,13] based on the flexible standard protocols published by the Brigham and Women’s Hospital (BWH) [9]. We studied concomitant drugs separately [5,14]. We used no additional premedication for RDD, only the standard premedication for each drug as per institutional protocols for standard infusions [2,12,15]. In the case of a reaction, we reassessed based on in vivo and in vitro biomarkers and considered making personalized adjustments to the second RDD (customized premedication or prophylactic drugs, decelerating dose escalation, additional solutions, or temporary dose reduction) [2].

Both DPT and RDD were carried out in a dedicated area within the inpatient infusion center set up as the Allergy Day Case Unit, which is equipped with all the necessary resources for anaphylaxis, including rapid intensive care access, a 1:2 nurse:patient ratio, and an allergist at the bedside [2,6].

During this 15-month period, we tested the 93 patients referred to us (55 women and 38 men). All patients had malignancies, mainly colorectal cancer (29%), breast cancer (15%), ovarian cancer (13%), lung cancer (10%), and cervical cancer (4%). The culprit drugs are shown in the Figure. The initial reactions were mild in 38% (35/93) of the patients, and all of them were immediate.

ST was positive with the culprit drug in 43% of patients (40/93). Up to 67% (32/48) of platin-reactive patients had positive ST results, with 24 oxaliplatin-positive patients (all in IDT, except for 1 SPT), 7 carboplatin-positive patients (5 IDT, 2 SPT), and 1 positive IDT to cisplatin. Only 4 taxane-reactive patients had a positive ST result (3 to paclitaxel and 1 to docetaxel), and there were 3 positive IDTs to rituximab and 1 to cetuximab.
DPT was performed in the 23 low-risk patients who had a mild initial reaction and negative ST results (25% of all referred patients) (Figure). Most results were negative (22/23); the only positive result was in an oxaliplatin-reactive patient, who experienced a moderate reaction (grade 2 Brown, grade 1 leucovorin, 1 dacarbazine). Only 1 patient experiencing a moderate reaction, which should be easily controlled at any highly specialized allergy center.

**Previous Presentations**

Data from this manuscript were presented in part in a poster session at the annual meeting of the Sociedad Española de Alergología e Inmunología Clínica (SEAIC), Gran Canaria, Spain, 2019.

Data from this manuscript were presented in part in an oral abstract session at the annual congress of the European Academy of Allergy and Clinical Immunology (EAACI), London, UK, 2020 (digital congress).

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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