Current situation of carboplatin desensitisation protocols in the hospitals of Spain

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ABSTRACT

Desensitisation protocols allow the continuation of treatment in patients who have presented hypersensitivity reactions. Carboplatin desensitisation solutions are usually prepared in the chemotherapy centralised units of hospital pharmacies and they are diluted under the established concentration limit to guarantee the stability of the preparation. An online survey was sent to hospital pharmacies, inquiring about local desensitisation protocols: reasons for use of desensitisation protocols, the protocols used and the stability given to carboplatin solutions. An important variability among the hospitals in carboplatin desensitisation practice was detected. Six different carboplatin desensitisation protocols were described and discordance with the storage period of the carboplatin solutions was observed. The lack of consensus on which protocol must be followed and data supporting the stability of the diluted product, contribute to distrust of carboplatin desensitisation protocols. Although the efficacy and safety of carboplatin desensitisation protocols has been widely demonstrated, many professionals still have concerns.

BACKGROUND

Carboplatin is the main drug used for the management of ovarian cancer, including advanced stage ovarian carcinoma and recurrent ovarian carcinomas in platinum-sensitive relapses.¹ One of the major clinical challenges in treating patients with relapse/recurrent ovarian malignancies is the high incidence of hypersensitivity reactions (HSRs) to carboplatin. Wide ranges of incidence have been reported from 1% to 35% depending on the severity and grade, being more frequent in patients with prolonged carboplatin exposure, with peak incidence at a median number of seven cycles.² Some of these HSRs could be serious and life-threatening,³ and the use of an alternative chemotherapy regimen is often limited by tumour sensitivity, lack of an effective alternative, poor tolerability or economic concerns.

Drug desensitisation allows continuation of treatment with carboplatin in patients who have presented HSRs.⁴ This methodology has emerged as a powerful tool for safely reintroducing medication that is beneficial for the management of patients with HSR.

Various desensitisation protocols have been implemented with a success rate of 80–100%.⁵ They enable the same platinum agent to be readministered by gradual reintroduction of small amounts of drug up to full therapeutic doses;

patients receive their target dose of medication in incremental steps.^{3,4,6} However, published protocols are heterogeneous, with variations in safety, administration times, number of dilutions, solvents, effectiveness and validation. In addition, a reasonable doubt about the stability of the diluted concentrations used in these protocols arises because there are no published data on carboplatin concentrations <0.5 mg/mL, the level indicated by the drug manufacturer.

Carboplatin stability seems to depend on concentration.⁷ Previous research showed that the stability of carboplatin solutions could not be guaranteed at a concentration of <0.2 mg/mL.⁸

OBJECTIVE

We aim to evaluate current practice in Spanish hospitals for carboplatin desensitisation protocols.

METHOD

A national, descriptive, cross-sectional and prospective study to evaluate the implementation of carboplatin desensitisation protocols in Spanish hospitals was designed.

An online survey was sent to hospital pharmacies, inquiring about local desensitisation protocols, through the National Society of Hospital Pharmacy (SEFH) and the National Working Group in Onco-Haematology Pharmacy (GEDEFO) mailing list.

The survey consisted of single-answer questions grouped into three categories: knowledge about actual carboplatin HSR rates and reasons for use of desensitisation protocols, protocols used at the institution and the stability given to carboplatin solutions prepared at the pharmacy.

Only one questionnaire was accepted from each hospital.

Descriptive statistics were used for analysis of results. Qualitative variables are presented by frequency analysis.

RESULTS

The survey was sent to approximately 200 Spanish hospital pharmacies with intravenous mixtures units; 49 completed responses were received from hospitals across Spain. Of these, 22 (45.8%) indicated that the prevalence of carboplatin hypersensitivity is uncommon ($\geq 1/1000$ to $<1/100$ cases) and 11 (22.4%) that it is rare ($\geq 1/10\,000$ to $<1/1000$ cases).

A total of 32 hospitals (65.3%) use local desensitisation protocols when HSRs occur, especially if no treatment alternatives are available.

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Table 1 Different carboplatin desensitisation protocols used in hospitals of Spain (n=32)

Desensitisation protocol	Frequency (%)
Three infusion solutions (1/100, 1/10 and 1/1) administered in 12 steps with a total duration of 6 hours	62.5
Four infusion solutions (1/1000, 1/100, 1/10 and 1/1): each solution is administered in 1 hour with a total duration of 4 hours	15.6
One infusion solution with a final concentration of 1 mg/mL with a total duration of 4.30 hours	9.4
Two infusion solutions (1/50 and 1/1): the first one is administered in 3 hours and the second, in 4 hours with a total duration of 7 hours	6.1
Five infusion solution (1/10000, 1/1000, 1/100, 1/10 and 1/1): each solution is administered in 30 min except for the last one which is administered in 1 hour with a total duration of 3 hours	3.2
Three infusion solutions (1/200, 1/20 and 1/1) administered in 12 steps with a total duration of 3.45 hour	3.2
Using a total dose of 500 mg calculated for a standard patient with a Creatinin clearance of 5 mL/min the concentration of the carboplatin solutions for the most common desensitisation protocol are: Solution 1/100: 5 mg/250 mL (0.02 mg/mL). Solution 1/10: 50 mg/250 mL (0.2 mg/mL). Solution 1/1: 500 mg/250 mL (2 mg/mL).	

Six different carboplatin desensitisation protocols were described by respondents (table 1). Most of them (62.5%) comprise three solutions diluted in 250 mL of dextrose 5%, administered in 12 steps with a total duration of 6 hours, as described by Castells *et al.*⁶

The solutions are always prepared in the chemotherapy centralised units of hospital pharmacies. In most institutions, the carboplatin is diluted more than 12 hours before administration (46.9%) whereas, in others (31.2%), dilutions are made just before administration owing to lack of stability information.

Most pharmacies (80.6%) prepare carboplatin solutions below the lower limit of dilution stated by the manufacturer (0.5 mg/mL). Maximum storage period is the same as for standard carboplatin dilutions, >24 hours, in most cases (59.9%).

The main reasons for lack of desensitisation protocols for carboplatin in pharmacies are staff and resources shortages (58.8%), followed by a lack of stability information (11.8%).

CONCLUSION

Our results show an important variability among the hospitals within a single nation for current carboplatin desensitisation practice.

The most commonly used protocol is based on three bags and 12 steps, with 3×10-fold diluted solutions at escalating rates,⁶ but individualisation may be appropriate in patients with severe HSRs and anaphylactic reactions using desensitisation with 16 steps (four bags) or 20 steps (five bags).

Although the stability of carboplatin has been extensively researched and documented, carboplatin 0.5 mg/mL solution has been the minimum concentration studied.⁹ In most cases, the concentrations used in carboplatin desensitisation protocols are below the stability limit stated by the manufacturer. Thus, stability tests should be carried out to confirm the stability of diluted carboplatin at concentrations below this threshold, and the minimum concentration of carboplatin solution which could guarantee stability still must be elucidated.

Other shorter protocols have also been successfully used. Furthermore, to deal with the potential problem of stability, other approaches suggest using protocols based on a multistep infusion of a single solution with a concentration of 1 mg/mL, ensuring the stability.^{10 11} These protocols avoid potential problems with multiple dilutions, use of unapproved minimum concentrations and the need for multiple bags of carboplatin to complete the required dose. Although this protocol seems to be effective and safe, it has been reported in very few patients and data are still insufficient to standardise this use. These new shorter protocols with only one or two bags should be used with extreme caution in highly sensitised patients, since these protocols are empirical and not based on in vitro or animal data, and their success may depend on the target patient population.¹²

The lack of consensus about which protocol must be followed and data supporting the stability of the diluted product, together with the possibility that the administration of carboplatin to patients who have developed hypersensitivity might have life-threatening consequences, contribute to the concerns of many professionals about carboplatin desensitisation protocols. Nevertheless, efficacy and safety has been widely demonstrated.

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