Carboplatin’s fourth decade: still searching for its sweet spot

Carboplatin, also called JM8, was characterized in preclinical testing in the 1970s as being potentially less nephrotoxic and emetogenic that cisplatin. Initial phase I studies were done with dose escalations calculating the dose based on body surface area and defined dose-limiting toxicity at a dose of ~400 mg/m² every 21–28 days as myelosuppression, predominantly thrombocytopenia, but which was dependent on patients’ renal function [1, 2]. The dosing of carboplatin in clinical practice was rendered unique by the work of Hilary Calvert and others in producing a nomogram for dosing the drug based on myelosuppression and renal function [3]. This has been widely adopted so that most oncologists using carboplatin formulate dose based on a calculated area under the concentration/time curve (AUC; milligrams of carboplatin per ml/min derived from the patient’s renal function rather than based on calculated body surface area as is the norm for many cytotoxic drugs). Many oncologists used and still use other formulae to calculate the creatinine clearance incorporating serum creatinine, weight and age. This approach was promoted using ‘chemotherapy calculation slide rules’ in the 1980s with transition to online calculators more recently. Some oncologists do a more formal and accurate measurement of the creatinine clearance using a 24-h urine collection or using the radionuclide-labeled ligand such as [99mTc]-DTPA to assess glomerular filtration rate (GFR) method to place into the Calvert formula but these are more costly and logistically difficult for the patient.

The work by Calvert and colleagues defined the risk of significant thrombocytopenia in single-agent carboplatin doses designed to produces AUCs in the range from 4–6 and 6–8 mg/ml for patients with a measured GFR range of 33–135 ml/min. Doses of carboplatin are calculated in milligrams by adding 25 to the GFR and then multiplying by the target AUC. Before this work, trials had been designed to test the substitution of carboplatin 500 mg/m² (generally equivalent to target AUC in the lower 4–6 mg/ml range) in each cycle for cisplatin combined with etoposide in regimens for advanced germ-cell tumors. The carboplatin regimen was definitively inferior for relapse-free survival in good risk category advanced patients [4], leaving cisplatin as the standard. Despite this carboplatin was developed in combination with etoposide in higher dose protocols (carboplatin 2100 mg/m² or AUC target 21–24 mg/ml in three divided doses on three successive days every 14–21 days) for poor risk and relapsed patients with positive results including a high proportion of complete responders and long-term disease-free survival as the second and third line of therapy, who are likely cured [5–7]. There is also a suggestion that such high-dose therapy may be more beneficial for patients with recurrent seminoma rather than patients with nonseminoma [8].

Concurrently, in the adjuvant setting for patients with early-stage seminoma and no evidence of lymph node or distant metastases the use of limited aortic field radiation therapy as the standard was being challenged. The MRC TE19/EORTC 30982 study was a noninferiority trial comparing standard adjuvant radiation therapy to single-dose, single-agent carboplatin with a target AUC of 7 mg/ml for patients with stage I seminoma [9]. Carboplatin was found to be noninferior to radiation treatment with a significant reduction in the risk of contralateral testicular primary cancers and no difference in toxicity or risk of secondary malignancy. There was some variation in dose given with patients using a calculated GFR mandated a 10% dose reduction compared with those with a GFR directly measured. Results from this study suggest a trend toward poorer disease-free outcome for the calculated versus the measured groups. This trend infers that precise carboplatin dosing may be important in this setting and, in particular, that under dosing may be detrimental.

In this edition of *Annals of Oncology*, Fehr and colleagues present data on the use of carboplatin as adjuvant therapy for 426 patients with early-stage seminoma who were at moderate risk of recurrence [10]. They used [99mTc]-DTPA to measure the GFR for every patient and then calculated how the dose would vary if formulae were used instead. Across the whole cohort, lower doses of chemotherapy would have been given had the GFR been calculated rather than measured. The level of under dosing varied based on the GFR formula used and is consistent with findings from a recently published cohort from Scotland [11].

Clinical practice is still to discuss three options with these patients: adjuvant para-aortic external beam radiation therapy, close observation with cross-sectional imaging and serum tumor makers or use of single-agent carboplatin. Preference has evolved toward observation from radiation therapy in the last decade because 80% of patients in this group never relapse and radiation carries with a small but definite risk of secondary malignancy. Carboplatin may also increase the risk of a secondary cancer but the data from large studies still lack sufficient follow-up for us to determine this.

In a patient where the selected treatment is adjuvant carboplatin, should we undertake formal creatinine clearance calculation on every patient getting adjuvant carboplatin for early-stage seminoma? This would be one approach but may not be necessary. If one examines the subsets analyzed by the authors, there is minimal variation in dosing for calculated GFR in patients <39 years old or with a body mass index (BMI) >30. Most of the inaccuracies occur in patients that are older than 40 years or are not obese. In this exercise, issues related to BMI are somewhat nebulous and difficult to apply. On the other hand, while these data are hypothesis generating and should ideally be confirmed, I will change my practice for patients 40 years and older and obtain [99mTc]-DTPA measurement of GFR and use it to calculate carboplatin dose.

One of my mentors once told me that it only took 60 years for us to learn how to use methotrexate correctly. This statement pertained to stopping joint erosion in rheumatoid arthritis when giving methotrexate on a weekly schedule; however, it translates well into the oncology area. In an age of molecular targeted putative novel agents, we should not lose sight of the need for optimal uses of older
agents, where incremental data can help define best practice even if individual clinical trials may not always be practice changing.

D. I. Quinn*

Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, USA
(*E-mail: diquinn@med.usc.edu)

disclosure

The author has declared no conflicts of interest.

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Risks of the new EU Data protection regulation: an ESMO position paper endorsed by the European oncology community

On 12 March 2014, the European Parliament voted on its position on the new European Union (EU) proposal for a General Data Protection Regulation, which will be now negotiated among the European Parliament, the Council of the European Union and the European Commission [1]. The final text will set the rules under which personal data are to be handled in the EU. It will thus affect many areas of our everyday life, including health and research. The cancer community is deeply concerned about unintended consequences of the current wording of the draft Regulation [2], which may put at stake the survival of retrospective clinical research, biobanking, and population-based cancer registries in the EU. In fact, the EU Parliament’s recent Resolution [3] on the Regulation imposes, or may be interpreted as imposing, the requirement for researchers to ask for a patient’s ‘specific’ consent every single time new research is carried out on already available data and/or tissues. This would lead to the necessity of researchers continuously asking patients to ‘re-consent’ for every single use of their data. In fact, the European Parliament’s Resolution [3], Amendment 191 states that,

1b. Where the data subject’s consent is required for the processing of medical data exclusively for public health purposes of scientific research, the consent may be given for one or more specific and similar researches. However, the data subject may withdraw the consent at any time.

Likewise, it would hinder the very collection of vital health information by requiring consent for the recording of data in population-based disease registries, which by definition need be all-inclusive, i.e. must collect all of the data of all individuals belonging to a given population. Amendment 191:

2. Processing of personal data concerning health which is necessary for historical, statistical or scientific research purposes shall be permitted only with the consent of the data subject, and shall be subject to the conditions and safeguards referred to in Article 83.

2a. Member States law may provide for exceptions to the requirement of consent for research, as referred to in paragraph 2, with regard to research that serves a high public interest, if that research cannot possibly be carried out otherwise. The data in question shall be anonymised, or if that is not possible for the research purposes, pseudonymised under the highest technical standards, and all necessary measures shall be taken to prevent unwarranted re-identification of the data subjects. However, the data subject shall have the right to object at any time in accordance with Article 19.

This text now forms the official position of the European Parliament. On behalf of the European oncology community, the entities endorsing this position paper would like the ongoing legislative negotiation process on the draft text to find the right balance to fully protect the privacy of patient data,