EDITORIAL

Thoracic malignancies, cisplatin and renal function

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Cisplatin (cis-dichlorodiammine-platinum II or CDDP) is the central drug used in the management of thoracic malignancies. The first trials were published in the 1970s [1], showing activity in lung cancer. Since then it has been shown to improve survival in advanced nonsmall cell lung cancer (NSCLC) [2] and survival and cure in combination with radiotherapy in locoregional NSCLC and prior to [3] or after resection in early NSCLC [4]. It is also a key drug in association with etoposide [5, 6] in the treatment of small cell lung cancer (SCLC), where it significantly improves survival. In mesothelioma, it has been shown to be the most active drug [7, 8].

The toxicity profile of cisplatin is unique. Dose-limiting toxicity is not haematological as with cytotoxic chemotherapy, but renal with the development of acute renal failure. The administration of higher doses of cisplatin (100–120 mg·m⁻²) with a better therapeutic index has been made possible by mannitol-induced diuresis and hyperhydration [9]. Nevertheless, the use of such dosages is associated with chronic toxicity with not only renal but also auditive neurological impairments, preventing long-term treatment as shown in a phase II randomised trial [10]. In this study, conducted by the European Lung Cancer Working Party (ELCWP) in patients with advanced NSCLC, high-dose cisplatin (120 mg·m⁻²) was compared to moderate-dose cisplatin (60 mg·m⁻²) plus carboplatin (200 mg·m⁻²) [10]. High-dose cisplatin was significantly associated with more renal (36% *versus* 19%), auditive (16% *versus* 4%) and neurological (16% *versus* 0%) toxicity without significantly different response rates (21% *versus* 23%).

Various attempts have been made in order to reduce or avoid the renal toxicity of cisplatin without reducing its effectiveness. Carboplatin, another platinum derivative with reduced nephrotoxicity, has been proposed as a substitute of cisplatin. Comparison of the two drugs in NSCLC has been the topic of 10 published randomised trials and three meta-analyses summarised in a recent review [2]. In randomised trials, the trend was in favour of cisplatin, both in terms of response and survival. The meta-analyses confirmed this impression; the results were statistically significant in favour of cisplatin if the analysis was restricted to the regimens using new drugs combined with platinum derivatives. Thus, cisplatin should be preferred to carboplatin because of a better survival effect.

Data are too limited to propose this approach for SCLC and mesothelioma. A second approach to increase platinum doses is to combine cisplatin with carboplatin, two drugs with different toxicity profiles. The theoretical advantage of such a regimen is to allow administration of higher dose-intensity of platinum derivatives than low-dose cisplatin alone. This hypothesis was also tested by the ELCWP [11] in a phase III randomised trial conducted in patients with metastatic NSCLC. In association with mitomycin (6 mg·m⁻²) and ifosfamide (3 g·m⁻²), the combination of moderate dosages of cisplatin (60 mg·m⁻²) and carboplatin (200 mg·m⁻²), CarboMIP regimen, was compared with cisplatin (50 mg·m⁻²) alone, MIP regimen. The study failed to demonstrate a significant improvement in response or survival but toxicity, mainly haematological, was higher with the CarboMIP regimen. A third method is the use of so-called low dosages of cisplatin. Five randomised trials have been performed on this [2]. None were able to report a significant advantage in favour of high dosages of cisplatin (100–120 mg·m⁻²) in comparison to lower dosages (50–60 mg·m⁻²).

All these studies were based on the assessment of renal function by creatinine clearance. Indeed, the determination of serum creatinine level is not sufficiently sensitive to evaluate the renal function at initiation or during any chemotherapeutic treatment. The determination of the glomerular filtration rate is mandatory. This parameter is reflected by the creatinine clearance measured from 24 h urine collection or calculated using the Cockcroft–Gault formula or the abbreviated Modification of Diet in Renal Disease formula [12]. This is particularly helpful in elderly patients with pre-existing chronic kidney disease (CKD), most often associated to cardiovascular comorbidities such as diabetes, ischaemic heart disease and/or hypertension. In these complex clinical situations, pharmacokinetic profiles of many drugs are disturbed and dosage adaptations remain difficult in daily practice. Moreover, pre-renal failure due to extracellular fluid depletion (poor intake, vomiting, diarrhoea, sepsis, *etc.*) is also commonly observed. Drugs themselves may trigger or worsen hypovolemia, *e.g.* non-steroidal anti-inflammatory drugs, by vasoconstricting afferent glomerular arterioles.

The prevalence of CKD in cancer patients is not well-defined. In a French retrospective study performed on a group of 4,684 cancer patients, LAUNAY-VACHER *et al.* [13] found that almost three fifths of patients (57.4%) suffered from a mild-to-moderate renal insufficiency (defined as a reduced glomerular filtration rate between 60 and 90 mL·min⁻¹·1.73 m⁻²), although only 7.2% exhibited an increase in serum creatinine (>1.1 mg·dL⁻¹). Of the 7,181 anticancer drug prescriptions, 53.4% required dosage adjustments for renal insufficiency. Of the patients treated, 80%

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received at least one such drug. The authors concluded that CKD was quite common in patients with cancer, and that drug dosage adjustments were often necessary.

In this issue of *European Respiratory Journal*, MATHÉ *et al.* [14] retrospectively evaluated the impact of cardiovascular comorbidities on cisplatin nephrotoxicity in patients over the first to fourth cycles of cisplatin. These investigators show that cisplatin-induced nephrotoxicity was significantly enhanced in the case of underlying hypertension and ischaemic heart disease, even more so if diabetes was also involved. Taking into account that in most kidney diseases long-term outcome is determined by the severity of the tubulo-interstitial damage, it appears crucial to provide the clinician with accurate tools for monitoring the extent of tubulo-interstitial lesions prior to and during any chemotherapy. Urinary biomarkers have been developed for several years and should become more and more attractive in the very near future, for at least three reasons [15, 16]. 1) Being well categorised by nephron segment they are able to specifically and quantitatively reflect any suspected insult. 2) Their longitudinal monitoring should predict progression of tubulo-interstitial lesions. 3) The impact of therapeutic strategies on their urinary excretion rate would be directly related to any prognosis of kidney function. Besides the well-known urinary excretion of low-molecular weight ("tubular") proteins, more recent urinary biomarkers demonstrated potential value in the management of CKD but also in unmasking early transient acute kidney injury. For example, kidney injury molecule-1 is a transmembrane glycoprotein upregulated in dedifferentiated proximal tubule epithelial cells and shed in urine following acute injury [17]. Urinary neutrophil gelatinase-associated lipocalin is not only associated with loss of kidney function but is also one of the earliest proteins induced in the kidney after an ischaemic or toxic insult [18]. Its long-term monitoring should help in measuring the response to nephroprotective treatment. Associating the measurement of albuminuria and urinary N-acetyl- β -glucosaminidase is suggested by some authors in an attempt to better predict diabetic nephropathy [19]. It is important to note that long-term studies will be necessary to validate specific biomarkers panels in CKD patient populations, particularly in the field of renal inflammation and/or fibrosis.

In conclusion, the renal management of cancer patients is a key process with many potential developments in the very near future. Characterisation and validation of highly sensitive and specific urinary biomarkers should optimise our understanding of the pathophysiology of renal diseases and our capacity to predict any earlier kidney injury. Furthermore, it would enhance the development of more targeted interventions. By minimising nephrotoxic insults induced by chemotherapeutic agents, these measures should hopefully improve the survival rate of cancer patients.

STATEMENT OF INTEREST

None declared.

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