Optimisation of chemotherapy in the era of immunotherapy

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Even in the era of immuno- and personalised therapy, optimal use of old-fashioned chemotherapy is of utmost importance, also for patients with renal insufficiency or declining renal function
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Even in the era of immunotherapy and personalised medicine, chemotherapy remains a cornerstone in the treatment of nonsmall cell lung cancer (NSCLC) [1]. Chemotherapy improves the length and quality of life of patients with metastatic disease for tumours both with and without oncogenic drivers. Chemotherapy in combination with checkpoint inhibitors is about to become the most effective first-line therapy for NSCLC [2]. Also in the adjuvant setting, *i.e.* adding chemotherapy after surgery, chemotherapy improves survival with an absolute increase of 4% at 5 years [3].

The optimal use of chemotherapy is an important factor in optimising the prognosis for patients. The fear of, or actual occurrence of, side-effects might interfere with its optimal use. A common complication of chemotherapy is the development of renal failure. The decline in renal function can occur as a direct toxic effect of the chemotherapeutic agent, but also patient-related and other drug-related factors play pivotal roles [4]. Nephrotoxicity often is a reason of treatment discontinuation or dose reduction resulting in a suboptimal treatment schedule [5]. The fact that about 60% of the people with cancer have underlying compromised renal function stresses the importance of this topic [6].

In this issue of the *European Respiratory Journal*, Visser *et al.* [7] describe the impact of pemetrexed on the renal function of patients with NSCLC. Pemetrexed is a therapeutic option for many patients. It is currently approved for treatment of nonsquamous NSCLC and mesothelioma. The approval for nonsquamous NSCLC involves first-line therapy in combination with cisplatin, and more recently in combination with carboplatin and pembrolizumab, as continuation and switch maintenance treatment and second-line therapy. In mesothelioma, the pemetrexed–cisplatin combination is the only approved regimen [8].

In the currently approved dose of 500 mg·m^{-2}, pemetrexed pharmacokinetics are linear. It is eliminated *via* the kidneys, with 70%–90% of the administered drug recovered in the urine within 24 h [9], it shows a biphasic elimination, and pemetrexed clearance linearly correlates with creatinine clearance [10, 11]. Systemic exposure is importantly correlated with toxicity and efficacy [12, 13], with a higher exposure leading to a higher incidence of dose-limiting haematological toxicity [10]. Renal function and dose of pemetrexed are the sole determinants for total systemic exposure [10, 14, 15].

Although nephrotoxicity is not amongst the list of dose-limiting toxicities of pemetrexed [16], it is commonly encountered. Pemetrexed enters the proximal tubule cells both *via* the basolateral and the

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apical side. Inside the cells pemetrexed is polyglutamylated, which impairs transport of pemetrexed out of the cell and results in raised intracellular concentrations. The inhibition of enzymes involved in the folate pathway by pemetrexed, impairing DNA and RNA synthesis of the tubule cells, further adds to the nephrotoxic effect of pemetrexed [4].

Presently, Visser *et al.* [7] showed in their prospective study, which was performed in a standard hospital setting, that patients with an estimated glomerular filtration rate (eGFR) of <90 mL·min^{-1} prior to the treatment with pemetrexed were at increased risk to develop acute kidney disease. The authors were able to confirm this observation in an independent retrospective cohort of NSCLC patients. Both cohorts also showed that a decrease in renal function during first-line pemetrexed–platinum treatment predicted for the development of renal disease during maintenance pemetrexed. During the maintenance treatment, almost 30% of the patients developed a decline in renal function, of whom 60% had to stop chemotherapy. The authors also noticed a statistically nonsignificant relationship between the cumulative dose of pemetrexed and nephrotoxicity.

It is obvious that renal toxicity has more impact on patients with a pre-existing impaired renal function. Whether this patient population also were more likely to develop significant nephrotoxicity has already been suggested in other studies. The paper by Visser *et al.* [7], however, is the first to show the predictive properties of baseline reduced eGFR and reduced renal function during therapy for a (further) reduction in renal function due to pemetrexed. This is in line with a similar French study which had shown that renal toxicity was the main reason for interruption of treatment with pemetrexed and bevacizumab [17].

The study by Visser *et al.* [7] has limitations, related to its partially retrospective design, the fact that the effect of pemetrexed was studied when given in combination with the nephrotoxic agents carboplatin and cisplatin, the lack of data on concomitant medication, and the relatively small number of patients. Nonetheless, the study paves the way for new strategies and research ideas and once again underlines the importance of optimal treatment for all patients, including those with a renal impairment.

A way to improve care for this friable population might be a change of our standard dosing practice. The current, standard practice of pemetrexed dosing on body surface area, by which the renal function is not taken into account, confronts the clinicians with two major problems: 1) a potentially effective treatment is withheld from patients with an eGFR <45 mL·min^{-1} [11]; and 2) deterioration of renal function as a result of pemetrexed treatment, leading to adverse effects and cessation of the treatment [11, 18], might prevent optimal anti-tumour therapy, as is also shown by Visser *et al.* [7]. This applies both to those patients with normal renal function and to those patients with a diminished renal function at the start of therapy [4, 9].

New studies on individualised pemetrexed dosing in patients with NSCLC and mesothelioma based on their renal function are, therefore, being eagerly awaited, also in the new immunotherapy era, in which triple combinations of chemotherapy and immunotherapy are about to become standard of NSCLC care.

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