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Letters

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Feasibility of Dose-intensified Paclitaxel after Chemotherapy-induced Renal Insufficiency in a Patient with Renal Transplantation

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In a recent phase I study, paclitaxel in a dose-intensified, weekly fractionated schedule (90 mg/m^2×6 every 9 weeks) was recommended for phase II studies [1]. We used this regimen as second-line chemotherapy in patients with advanced breast cancer in a phase II study. Preliminary results of the first 43 patients (projected overall number: 50 patients) yielded an overall response rate of 34%. Haematological toxicity was very mild with only 0.6% of clinically relevant leucopenia WHO grade III.

We report the case of a 51-year-old breast cancer patient with liver and bone metastases who was treated in this study. She had undergone renal transplantation for polycystic kidneys 5 years prior to diagnosis of breast cancer. As first-line chemotherapy, the patient had been treated with vindesine (3 mg/m^2), epirubicin (100 mg/m^2) and cyclophosphamide (600 mg/m^2) (ViEC) every 3 weeks. During that treatment, her leucocyte count decreased to 1200 leucocytes/μl whilst the serum creatinine level had increased from 80 μmol/l (normal up to 90 μmol/l) before treatment to 128 μmol/l before the second cycle. This increase made a dose reduction of 25% necessary after which the creatinine level did not normalise (108 μmol/l at the end of treatment). The patient had started ViEC treatment with a creatinine clearance of 61 ml/min which decreased to 46 ml/min during the treatment and stayed at this level throughout the patient's lifetime. During ViEC chemotherapy, immunosuppressive treatment with cyclosporin A showed levels within therapeutic ranges. Cytomegalovirus antigen and serological status did not change either. The overall response to the ViEC treatment was a partial remission (complete regression of the liver metastases, no change of bone involvement).

After 2 months without cytotoxic treatment, the patient again showed progressive liver metastases and was enrolled into the phase II study with dose-intensified fractionated paclitaxel as described above. During this treatment, she again showed a complete regression of liver metastases without experiencing any impairment of renal function. She had started with an elevated baseline creatinine level of 109 μmol/l and ended up with normalisation of the creatinine level to 90 μmol/l by the end of the first cycle. Bone marrow suppression was mild with the leucocyte count always ranging between 3000 and 4000/μl. The low haematological toxicity profile under weekly fractionated paclitaxel was advantageous, as the patient was under immunosuppressive therapy after organ transplantation with an increased risk of infectious complications.

The compensated renal insufficiency under first-line chemotherapy with ViEC was interpreted as toxicity from cyclophosphamide medication. Cyclophosphamide is known not only to cause haemorrhagic cystitis but also renal damage [2]. It is a prodrug which is anabolised to the active compound in the liver. Approximately 20% of the original drug and 60% of the active metabolites are eliminated by the kidneys with the urinary metabolite concentration increasing in the renal tubular system due to reabsorption of water. The highest concentrations are reached in the bladder leading to haemorrhagic cystitis.

When the patient relapsed, we tried to avoid schedules containing alkylating agents or methotrexate as second-line chemotherapy for fear of further deterioration of renal function. Paclitaxel seemed appropriate as 95% is metabolised in the liver whilst only around 5% is secreted by the kidneys [3]. Thus, paclitaxel can even be given in acute renal failure in patients on haemodialysis [4, 5].

In conclusion, the absence of renal toxicity makes paclitaxel an important treatment option in patients with impaired renal function. This is especially true for ovarian carcinoma in which paclitaxel-based schedules are generally accepted as first-line treatment and where deterioration of renal function due to peritoneal carcinosis is a frequent complication.

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