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Perspectives and Commentaries

Nephrotoxicity of Chemotherapy

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CHEMOTHERAPY-RELATED nephrotoxicity is a well-known problem in medical oncology [1, 2]. In cancer patients, however, one must always be aware of possible additive and synergistic effects that may potentiate chemotherapy-induced renal injury [3]. These patients may reveal hypovalemia or reduced cardiac output, inducing renal hypoperfusion; they may suffer from neoplastic renal infiltration and more frequently tumor-related obstructive nephropathy; they may also develop cancer-related microangiopathic hemolysis, disseminated coagulopathy and renal vein thrombosis. Cancer patients may reveal immunecomplex-mediated glomerulopathy, minimal change nephritis, renal amyloidosis and more frequently renal tubulopathy due to Bence-Jones proteinuria. Cancer patients are frequently treated with other nephrotoxic drugs such as aminoglycosides, amphotericin B and nonsteroidal anti-inflammatory drugs; they may suffer from radiation induced nephritis as well as from renal toxicity related to iodine contrast media. Urinary tract infections are a frequent problem in these patients as well as several metabolic complications such as hypercalcemia, hyperuricemia and, more rarely, lysozymuria. All these factors should be looked for when chemotherapy related nephrotoxicity is suspected.

Antineoplastic agents with well-established renal toxicity are: methotrexate, cisplatin, methyl-CCNU, streptozotocin, mithramycin and mitomycin. The nephrotoxicity of methotrexate and cisplatin has been well studied and is preventable at the present time by correct patient management such as forced diuresis and urinary output monitoring. For both these drugs urinary clearance is high and direct toxicity to the renal tubule has been demonstrated [1, 4]. It is clearly related to concentration, duration of exposure and solubility of the drug and therefore depends on various factors influencing these variables. There is no clear cumulative nephrotoxicity of these drugs in the managed patient.

Drug-related nephrotoxicity is less well understood in connection with other agents such as methyl-CCNU, streptozotocin, mithramycin and mitomycin. In the case of methyl-CCNU, a cumulative toxicity pattern has been established with a median cumulative nephrotoxic dose near to 2000 mg/m^2 [5]. The mechanisms remain unclear and the best protection is a limitation of the dose to less than 1200 mg/m^2. Nephrotoxicity of streptozotocin, another nitrosourea, does not show a cumulative toxicity pattern; nephrotoxicity seems to be related to high single doses. Treatment discontinuation when proteinuria appears and doses no higher than 1.5 g/m^2/week are recommended [1].

Mitramycin-associated nephrotoxicity is also schedule-dependent and appears to be cumulative to some extent [1]; with brief courses of treatment and with low doses (25 μg/kg/day for 3 days) this agent loses much of its renal, hematological and hepatic toxicity.

Mitomycin nephrotoxicity is the subject of a report by Verwey *et al.* in this Journal [6]. Among renal injuries related to chemotherapy, mitomycin nephrotoxicity is probably the most ambiguous one. This problem has been variously described as microangiopathic hemolytic anemia [7],

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hemolytic–uremic syndrome [8], renal disease after mitomycin C therapy [9]. The clinical syndrome shows variable combinations of microangiopathic hemolytic anemia, thrombocytopenia, hematuria, renal failure, systemic arterial hypertension, non-cardiogenic pulmonary edema and, more rarely, congestive heart failure or neurologic abnormalities [10, 11]. Pathological findings at autopsy generally consist of thrombotic microangiopathic lesions in the kidney with glomerular infarction due to fibrin thrombi in the afferent arterioles and glomerular capillary loops. Fibrinoid necrosis and intimal hyperplasia have been described in the afferent arterioles together with congestion of glomerular loops and interstitium [10]. Similar vascular lesions have also been described in the pulmonary system. Several clinical and pathological similarities exist with cancer-related microangiopathic hemolytic anemia as well as with the classical hemolytic–uremic syndrome and with thrombotic thrombocytopenic purpura [11]. The pecularity of this syndrome, however, is its significant relationship to mitomycin use [6, 12]. Another is its close relationship to tumor histology, the syndrome being most often described in digestive adenocarcinomas, suggesting a possible tumor-specific relationship [10]. On the other hand, the same syndrome has also been described in patients not treated with mitomycin as well as in patients on adjuvant treatment and those with chemotherapy-induced complete remission of their disease [10]. The relationship to mitomycin and to the tumor itself remains therefore ambiguous. The relationship between the cumulative dose of mitomycin and its nephrotoxicity is not really evident. Unlike the situation observed in the case of methyl-CCNU, with mitomycin, the threshold dose is rather low (30–40 mg/m^2) and an upper limit, for which a cumulative nephrotoxicity appears in most of the treated patients, has not been described. Several other interesting observations have been made: blood transfusions have been shown to induce clinical deterioration of the patients, suggesting that blood products contain substrates that exacerbate the pathophysiological process [10, 11, 13]; elevated circulating immune complexes have been detected in the plasma of several patients [10]; these immune complexes were shown to induce *in vitro* platelet aggregation. Further analysis of these immune complexes revealed that they contained IgG antibody, complement and a glycoprotein antigen; the antibody could not be shown to react with mitomycin but showed significant binding to endodermally derived neoplastic tissue samples, suggesting a tumor-specific relationship. Thus mitomycin might be only a co-factor in the etiopathogenesis of the syndrome, the primary process implicating some tumor-specific immune reaction of the host with consequent activation of the coagulation cascade leading to microvascular lesions.

The disease, once established, is very difficult to stop; mitomycin withdrawal is generally ineffective but sometimes may prove useful. Treatment with antiplatelet agents and immunosuppressive drugs has generally been disappointing. A few patients have shown some response of the hemolytic process to plasmapheresis [11].

The best therapeutic results so far were obtained with extracorporeal protein-A immuneabsorbtion of immune-complexes [14]. This technique has permitted excellent control of all the hematological parameters in five out of five patient being treated and has assured stabilization of renal insufficiency. Until these techniques can be approved for general use, mitomycin-asociated hemolytic–uremic syndrome remains a highly lethal complication with an incidence of 2–10% and mortality between 50 and 100%. This is particularly distressing, as most patients are in partial or even complete remission of their disease.

What are then the recommendations that should be made? Above all, mitomycin should be used with caution for adjuvant therapy, particularly with adenocarcinomas. Administration of a cumulative dose above 30 mg/m^2 should only be considered if the drug has a clear therapeutic advantage. In those patients, hematuria, proteinuria, anemia and the presence of fragmented cells should be looked for and mitomycin therapy should be discontinued if the syndrome is suspected. Blood transfusions should be avoided or given with concomitant heparin infusion.

Basic research should go on to further elucidate this most fascinating, multifactorial etiopathogenic process; better understanding of what really happens may certainly provide valuable tools for better patient management.

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