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Is Kidney the Real Dose-limiting Organ after Total Body Irradiation and Bone Marrow Transplantation?

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INTERSTITIAL PNEUMONITIS (IP) is currently considered as the major dose-limiting late complication of total body irradiation (TBI) and bone marrow transplantion (BMT) and lungs are considered to be the main dose-limiting organ [1]. However, an increasing number of retrospective analyses of long-term survivors after TBI and BMT have recently revealed that renal dysfunction may, in fact, become a major and potentially lethal complication in these patients [2–4]. An incidence of detectable renal damage (e.g. doubling serum creatinine) as high as 53%, with 24% eventually requiring dialysis, has been reported [4]. As a consequence of these observations a few experimental studies have addressed the problem of kidney damage after BMT and have indicated an appreciable degree of damage in animals treated with different conditioning regimens followed by BMT [5–8].

Both clinical and experimental studies suggest that irradiation may be the major contributing factor causing this renal damage. Indeed kidneys are known to be a relatively radiosensitive organ [15]. A decrease in renal plasma flow and glomerular filtration rate has been observed after doses of radiation as low as 4 Gy [9]. However, radiation is only a part of the very complex treatment in BMT that may involve many other nephrotoxic factors. Based on a number of recent reports one may speculate that many of the factors known to participate in producing IP after BMT may, in fact, also be of importance for late kidney damage. Such factors include infections by agents common in the immune-suppressed patients such as cytomegalovirus [10] and fungal infections [4], drug toxicity, especially cyclosporin A [11] and amphotericin B [4], and enhancement of radiation damage by cytotoxic agents, e.g. cisplatinum and busulfan [5]. However, the relative importance of each of these factors and the contributions made by other clinical variables such as patients' age (the paediatric group of patients seems to be particularly susceptible to this complication) [12,13], graft vs. host disease, pretreatment renal function and other organ failures (e.g. liver) have not been systematically analysed.

The available data on kidney damage after the complex treatment of BMT are still far from being complete. Most of the experimental studies on kidney damage after radiation or combined radiochemotherapy have been done using isolated kidney irradiation and not TBI. Thus, they could not measure the possible indirect radiation effects on the kidney caused by TBI-induced tissue destruction elsewhere in the body [14,15]. Rats receiving lower half body irradiation exhibited less severe kidney damage than those receiving TBI [8]. On the other hand, we have noted that combined cyclophosphamide (CTX) and TBI resulted in a higher degree of lung damage than that obtained when CTX was given with thoracic irradiation only. To what extent this observation is applicable to the kidney is unknown but it may suggest a possibility of an increased sensitivity under TBI conditions to what was previously known as "safe" doses and thus partly explain the high incidence of kidney damage in patients having TBI and BMT.

On these grounds it should be emphasised that renal damage may now be a major dose-limiting and life-threatening complication in long-term survivors after BMT and that it is important to keep the possibility of a progressive kidney damage in mind before any intensification of the conditioning regimens (tempted by the success in preventing and treating IP) is considered or whenever a further treatment is needed for patients previously treated with BMT. Finally, this problem needs to be specifically looked for in order to reveal further information on the factors contributing to the renal dysfunction after TBI and BMT and their possible interactions.

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