Cancer and patients with end-stage renal failure

Recipients of renal transplants may acquire cancer by the accidental transplantation of cancer cells with a kidney taken from donors with cancer, by the growth of residual or metastatic tumour in patients with pre-existing malignancy, or by the de-novo formation of neoplasms some time after transplantation.1

An increased incidence of de-novo neoplasms has been reported1 2 in patients after renal transplantation, and the main factor responsible is thought to be the prolonged use of immunosuppressive drugs given to prevent rejection. Penn and Starzl1 reported 75 long-term survivors of organ transplantation who had developed de-novo neoplasms, including 16 of their own patients. The incidence of neoplasia was 80 times greater than in the average population in a comparable age range. Forty-four of the patients had epithelial tumours, including squamous-cell or basal-cell skin carcinoma (11 cases), in-situ carcinoma of the cervix uteri (eight cases), carcinoma of the lip (eight cases), and a variety of other tumours. Thirty-two mesenchymal tumours occurred in 31 patients, including 28 lymphomas. There were 21 patients with reticulum-cell sarcoma. Out of 27 patients with lymphoma, 14 had lesions of the brain or spinal cord, including 10 of the patients with reticulum-cell sarcoma.

The average time for appearance of the tumours was 29 months after transplantation, but in six patients it was less than four months after transplantation. One explanation for the early appearance of tumour in some patients is that a cancer had been present at the time of operation. Another possible factor considered by Penn and Starzl1 was that chronic renal failure may predispose to neoplasia because of the depression of immune responses in uraemia. In a study2 of over 6000 patients reported to a kidney transplant registry, Hoover and Fraumeni calculated that the risk of developing lymphoma after transplantation was about 35 times higher than normal, and that this was largely due to the particularly enhanced risk of developing reticulum-cell sarcoma, which was 350 times greater than expected. Skin and lip cancers occurred up to four times more often than expected and other tumours were two and a half times more common.

More recently reports have suggested an increased incidence of cancer in patients with chronic renal failure having maintenance haemodialysis who have not been given transplants and have not received any immunosuppressive drugs for their intrinsic renal disease.3-5 Matas et al4 found an increase in the incidence of relatively common mesenchymal tumours such as cancers of the breast and kidney, which contrasted with the increased incidence of epithelial and lymphoproliferative tumours after renal transplantation. Kinlen et al, however, studied 1651 patients from six dialysis centres in England over 10 years and could find an excess only of non-Hodgkin's lymphoma.6

The data on the increased incidence of malignancy in uraemic patients have been criticised as inconclusive. The reports from the National7 and European Dialysis Registries8 have been said to be inadequate because non-fatal cases were not reported and the length of exposure to uraemia and size of the population at risk were unknown.9 Lindner et al9 therefore studied 153 patients who had had long-term dialysis for an average of 66 months to determine the incidence and type of neoplasms and to compare these findings with cancer rates for the population in the same geographical area. Nine cancers were found among 148 men (six lungs, one kidney, one pancreas, one carcinoid). Eight of the nine men were smokers. This result was higher than expected (that is, 3-6 cases; p < 0-0137) for exposure-specific and age-specific controls of the same sex. The increase in the incidence of common tumours supports the findings of Matas et al4 and contrasts with the increase in the incidence of epithelial and lymphoproliferative tumours after renal transplantation. The reason for this difference is uncertain. Uraemic patients have defective humoral and in particular cell-mediated immunity,10 11 and loss of immunological surveillance may play a part in the increased incidence of common neoplasms in such patients. The renal transplant recipient differs from the uraemic patient in being subject to chronic stimulation by antigens, which appears to be important in the genesis of lymphoreticular neoplasms in animal models.12 13

The primary central nervous system lymphomas associated with organ transplantation are apparently of B-cell origin, and Epstein-Barr virus has been considered as a likely aetiological agent.14 After renal transplantation a substantial number of patients continue to have varying degrees of chronic renal failure not severe enough to necessitate dialysis but nevertheless possibly still having an adverse effect on immunological mechanisms. In patients having long-term dialysis who are exposed to large volumes of dialysis fluid two or three times a week another factor is the effect of various trace elements in the water used to prepare the dialysis fluid. Might some of these trace elements be carcinogenic? Among other possible influences is the geographical location of patients, and Shell et al15 have reported the effect of renal transplantation on the incidence of cancers in Australia. Owing to the oncogenic
effect of sunlight, 77% of their patients with cancer had skin cancer, but with an unusual distribution for Australia with squamous-cell carcinoma accounting for three-quarters of the cancers and basal-cell carcinoma for the rest. In the general population this ratio is reversed. Furthermore, the squamous-cell tumours in the transplant recipients were unusually aggressive.

The type of underlying renal disease may be important. An increased incidence of transitional-cell neoplasms of the renal pelvis has been reported in patients with analgesic nephropathy, and patients with polycystic kidneys may have a higher risk of kidney tumours. In some cases renal disease may be induced by extrarenal neoplasms; an association is well established between a nephrotic syndrome (usually due to membranous glomerulonephritis or a minimal-change type of nephropathy) and a variety of neoplasms.

What about treatment? Epithelial tumours of the skin, the lip, and the uterine cervix may be treated by conventional surgical or radiotherapeutic methods, and no reduction in immunosuppressive treatment is usually recommended. The prognosis for those with carcinoma of the abdominal and thoracic organs and with most mesenchymal tumours is poor, however, and drastic reduction or discontinuance of immunosuppressive treatment is usually thought necessary with an indefinite treatment in the incidence of graft rejection. Fortunately the overall incidence of neoplasia is still too low to be considered a contraindication to long-term dialysis and renal transplantation.

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7. Bryan FA. Seventh annual report of the National Dialysis Registry. 1975. (Research Task Force Institute Report No AK-7-7383.)

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Sodium cromoglycate in proctitis and ulcerative colitis

Most patients with symptomatic proctitis or distal ulcerative colitis respond rapidly to standard medical treatment including sulphasalazine and steroid-retention enemas. In some patients, particularly those intolerant of sulphasalazine, symptoms may be persistent, distressing, and difficult to relieve. Heatley and his colleagues argued that since exacerbations of ulcerative colitis may be mediated by a type 1 hypersensitivity reaction, which can be blocked in allergic asthma by sodium cromoglycate, the drug warranted evaluation in patients with ulcerative colitis. A small double-blind cross-over trial lasting six months in 12 patients with symptomatic ulcerative colitis suggested that treatment with sodium cromoglycate increased the patient's sense of wellbeing and was associated with improved sigmoidoscopic and rectal biopsy appearances.

More recently a much larger controlled trial of sodium cromoglycate (800 mg daily) failed to confirm these early findings; similar numbers of patients with symptomatic ulcerative colitis at the start of the trial improved, deteriorated, or maintained a steady state in both the treatment and placebo groups. The number of relapses among those patients who were in remission at the start of the trial was also similar in the treatment and placebo groups. In a separate study patients with ulcerative colitis in remission were allocated at random to receive either a low-dose or high-dose sodium cromoglycate regimen or sulphasalazine. The relapse rate was similar in the two groups receiving sodium cromoglycate, which proved considerably less effective than sulphasalazine in maintaining remission.

The evidence from relapse rates in these trials suggests that sodium cromoglycate is little more effective than placebo treatment—but this view has now been challenged in a recent study where the relapse rate for patients taking sodium cromoglycate was 40% compared with 75% in the placebo group. There is, however, general agreement that the addition of sodium cromoglycate to conventional treatment confers no additional benefit.

The place of sodium cromoglycate in ulcerative colitis seems limited. It may be worth trying in symptomatic patients who cannot tolerate sulphasalazine, though even in this group of patients evidence for its value is conflicting. Desensitisation is probably a more effective and practical approach for patients with sulphasalazine intolerance—and an encouraging prospect is on the horizon with tests of a new agent comprising two molecules of 5-aminosalicylate, the active component of sulphasalazine, from which sulphasalazine (which is responsible for sulphasalazine intolerance) has been eliminated.

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