The radical treatment of paraprotein disorders affecting the kidney

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When a paraprotein causes renal injury, cytotoxic treatment may be directed against the underlying plasma cell clone, in the hope of reversing, halting or minimizing the damage. Bolder, high-dose cytotoxic regimens are now being used for these disorders and are the subject of this review.

Multiple myeloma

Multiple myeloma is the classic disorder in which paraproteinaemia causes renal dysfunction. It is a malignant disease of plasma cells characterized by bone pain, anaemia, immunosuppression and renal impairment. Renal failure is present at the time of diagnosis in 20–30% of patients with myeloma, and is due mainly to the nephrotoxic effects of the abnormal immunoglobulin light chains [1], but may be exacerbated by hypercalcaemia, dehydration and drugs [2].

Conventional cytotoxic treatment for myeloma includes melphalan (with or without prednisolone) [3] or combination chemotherapy using regimens such as VAD (vincristine, adriamycin and dexamethasone) [4]. Randomized trials show combination chemotherapy to be superior to melphalan in terms of response rate, but equivalent in terms of life expectancy [4]. Chemotherapy results may be improved further by dose intensification with autologous bone marrow stem cell support. In a landmark study from the Intergroupe Français Myéline (IFM), patients under the age of 65 years (with normal renal function) were randomized between conventional chemotherapy and autologous bone marrow transplantation (ABMT) [5]. Patients in the ABMT arm were shown to have superior event-free and overall survival rates at 5 years of 28% and 52%, respectively, compared with 10 and 12% in the conventional treatment arm. Conventional chemotherapy followed by high-dose therapy (HDT) has now become the standard treatment in newly diagnosed myeloma patients. Peripheral blood stem cells (PBSCs) have succeeded bone marrow as the stem cell of choice, largely because of their more rapid engraftment kinetics [6]. Subsequently, the IFM have demonstrated that conditioning with melphalan 200mg/m² is at least as effective as the combination of melphalan 140mg/m² with total body irradiation used in their original study [6]. Recent data support the use of tandem high-dose procedures [7,8].

Initially, most centres offering this treatment excluded patients with renal failure. However, a number of reports described cases with renal failure in which a relatively successful outcome was achieved with HDT [9–11]. The main question about treating myeloma patients with renal failure with HDT is whether the toxicity of the treatment is increased, thereby risking the potential survival advantage. The Spanish ASCT registry reported the outcome after transplantation in 14 myeloma patients with renal failure. The treatment-related mortality (TRM) in this group was 29% compared with 3.4% in 552 patients with normal renal function at the time of transplantation [12]. Lower TRM rates have been reported by other groups, e.g. the Arkansas group reported the outcome in a series of 81 myeloma patients with renal failure at the time of HDT. This included 38 dialysis-dependent patients [13]. Because patients treated with 200mg/m² of melphalan suffered significant toxicity, subsequently patients received 140mg/m². If HDT was well tolerated, patients proceeded to a second transplant procedure. Patients receiving the higher melphalan dose, particularly those on dialysis, suffered the effects of increased toxicity, i.e. mucositis, pulmonary complications, atrial dysrhythmias and neurological side effects. The authors suggested that melphalan metabolism may be affected by the hypoalbuminaemia present in renal failure, since the drug is normally bound to albumin. Previous reports suggested that high-dose melphalan was metabolized adequately, even in patients on dialysis [14,15], but the Arkansas experience emphasizes the advice that melphalan dosage should be limited in renal failure. TRM was

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Primary amyloidosis

The success of HDT in myeloma has encouraged its use in primary amyloidosis, the condition in which an abnormal plasma cell clone leads to systemic deposition of AL amyloid [17]. Initial reports of HDT in amyloidosis revealed a high TRM with rates of 15–43% [18–20]. The major problems encountered with HDT were in patients with cardiac amyloidosis. Cardiac amyloid has even been reported to be associated with deaths following PBSC re-infusion [21].

Despite the high TRM, patients surviving the procedure have evidence of disease response. The Boston City Hospital Group reported 25 patients treated with high-dose melphalan and autologous PBSC re-infusion. At a median follow-up of 24 months, 68% of patients were alive and the median survival had not been reached. Two-thirds of surviving patients demonstrated an improvement in amyloid-related organ involvement [22].

There is some evidence that patients with predominantly renal involvement respond well to HDT. In an update of 102 patients treated at the Boston City Hospital in this way, it was shown that the survival of those with predominant renal involvement (median follow-up of 20 months) was 83% in those receiving 200 mg/m² of melphalan and 75% in those receiving a dose of 140 mg/m² [23]. In contrast, the Mayo Clinic report renal failure to be an adverse prognostic factor [24]. Of 66 patients with amyloidosis treated with HDT, nine patients (14%) died in the first 100 days following stem cell return. The actuarial survival at 24 months was 75%, with the number of organs involved being the single most important predictor of response. Although the median response time was 3.6 months, six renal patients took over a year to improve. In this series, the serum creatinine was found to predict for adverse survival. Nine patients required dialysis post-transplant, of whom seven subsequently died. Based on these data, it has been advocated that patients with a serum creatinine > 133 μmol/dl or whose creatinine clearance is < 51 ml/min should receive reduced dose therapy [25].

Although the existing data appear to support the use of HDT in selected patients with amyloidosis, caution should be exercised when interpreting the outcome data. Since most patients undergoing these procedures are highly selected, it is possible that they represent a good prognostic group whatever treatment they receive. In a review of patients on the Mayo Clinic database, it was found that, because of the stringent selection criteria, patients eligible for HDT fare as well with ordinary chemotherapy, the median survival being 42 months [25,26]. Data from the UK National Amyloidosis Centre also suggest that the results of VAD or C-VAMP regimens may be at least as good as those of autologous transplantation [27].

Other conditions

Light chain deposition disease (LCDD) results from the deposition of abnormal monoclonal light chains in the renal glomerulus, leading to renal insufficiency [28]. It may be part of true myeloma or an isolated monoclonal light chain disorder. Renal function has been shown to be improved by chemotherapy, but the potential role of HDT in this condition remains to be evaluated [29]. Lymphoplasmacytoid lymphomas may be associated with the production of a paraprotein, e.g. Waldenstrom’s macroglobulinaemia, but renal failure is uncommon [30]. Although HDT has been tried, it remains experimental [31].

The role of allogeneic bone marrow stem cell transplantation

Allogeneic bone marrow transplantation is an alternative to autologous stem cell grafting. Although allogeneic transplants for amyloid have been reported [32,33], there has been much more experience of this in myeloma. Allogeneic transplantation has the advantages that the source of the stem cells is free of contamination with myeloma, and that donor marrow has an immune-mediated anti-myeloma effect.
[34,35]. The problem with such procedures is the high toxicity associated with the conditioning protocols and the associated immunosuppression and graft-versus-host disease [36]. There are attempts to circumvent this by reducing the intensity of the conditioning protocols [34,37]. Reports of autologous stem cell transplantation followed by dose-reduced allogeneic transplantation have been particularly encouraging [38]. At present, there are insufficient data on the outcome following allogeneic procedures in myeloma patients with renal failure. One report of interest, however, is that of two myeloma patients with end-stage renal disease treated with a non-myeloablative preparative regimen with the aim of producing a mixed lymphohematopoietic chimerism of both donor and patient cells [39]. Such chimerism has been suggested to provide tolerance for solid organ allografts. The conditioning was followed by a combined HLA-identical sibling bone marrow and renal allograft from the patients’ sisters. The myeloma responded well, with both patients attaining complete remission. The renal allograft was well tolerated, with normal renal function persisting after the withdrawal of immunosuppression.

In conclusion, the use of HDT and autologous bone marrow stem cell transplantation now plays an important role in the management of myeloma and, to a lesser extent, amyloidosis. Such procedures may be used (with a degree of caution) in the setting of renal failure. Allogeneic bone marrow transplantation offers the potential of improving survival further, but refinement of these procedures is still required.

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Oligonephronia, primary hypertension and renal disease: ‘is the child father to the man?’

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In the US hypertension has been estimated to affect > 40 million, or ~24% of the population [1]. Numerous physiologic, biochemical, genetic, developmental and environmental factors, including socioeconomic, are felt to influence levels of blood pressure. However, the relative importance of these biologic and environmental forces and when in the course of human life they exert their influences are uncertain. It has been suggested that environmental forces occurring in early childhood, including those affecting intra-uterine growth and development, may pre-programme the organism for subsequent hypertension, cardiovascular and renal disease [2,3]. In this regard, a large body of evidence has demonstrated statistical associations between low birth weight and/or gestational age and hypertension, on the one hand, as well as cardiovascular and renal disease in adults and in children on the other [4–8]. A recent study by Keller et al. [9] showing an association between primary hypertension and reduced nephron number has further heightened interest in the possible relationship between low birth weight, hypertension and cardiovascular and renal disease risk.

Birth weight and nephron number

It has been proposed by Brenner and Chertow [10] that early gestational age and/or fetal growth retardation (FGR) might be associated with impaired nephrogenesis. The resulting reduced number of glomeruli might then serve to link the observed association of low birth weight with the subsequent development of increased childhood and adult blood pressure and increased risk for cardiovascular and renal disease in adults. They suggest that glomerular hyperfiltration resulting from reduced nephron number would stimulate physical and cellular factors leading to systemic hypertension, glomerular sclerosis and obsolescence, and progressive deterioration of renal function. Support for the idea that FGR is associated with a reduced post-natal number of nephrons comes from several observations. Studies by Hinchcliffe et al. [11,12] have shown that FGR was associated with significant reductions in nephron number. Similarly,