REVIEW ARTICLE

Drug Safety 2000 Aug; 23 (2): 101-113
0114-5916/00/0008-0101/$20.00/0

Post-Transplant Malignancy
The Role Of Immunosuppression

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Contents

Abstract

Immunosuppressed organ allograft recipients have a 3- to 4-fold increased risk of developing tumours, but the risk of developing certain cancers is increased several hundredfold. With the exception of skin and lip cancers, most of the common malignancies seen in the general population are not increased in incidence. Instead, there is a higher frequency of some relatively rare tumours, including post-transplant lymphomas and lymphoproliferative disorders (PTLD), Kaposi's sarcoma (KS), renal carcinomas, *in situ* carcinomas of the uterine cervix, hepatobiliary carcinomas, anogenital carcinomas and various sarcomas (excluding KS). Skin and lip cancers present some unusual features: a remarkable frequency of KS, reversal of the ratio of basal to squamous cell carcinomas seen in the general population, the young age of the patients, and the high incidence of multiple tumours (in 43% of the patients). Anogenital cancers occur at a much younger age than in the general population. Salient features of PTLD are the high frequency of Epstein-Barr

‡Dr Israel Penn, an outstanding tutor who received numernous honors, died on 18 November 1999 from a B cell lymphoma. Ironically, this was a tumour about which he had written frequently. He started a tumour transplant registry in 1968, and through his own efforts gathered information on more than 15 200 cancers in transplant patients throughout the world, establishing the incidence and consequence of malignant tumours in patients receiving immunosuppression for organ transplantation.

virus-related lesions, frequent involvement of extranodal sites, a marked predilection for the brain and frequent allograft involvement.

As the immunosuppressed state *per se* and various potentially oncogenic viruses play a major role in causing these cancers, preventative measures include reducing immunosuppression to the lowest level compatible with good allograft function and prophylactic measures against certain virus infections. Reduction of exposure to sunlight may also decrease the incidence of skin cancer. In addition to conventional treatments (resection, radiation therapy, chemotherapy) patients may receive antiviral drugs, interferon-α and various other manipulations of the immune system. A significant percentage of cases of PTLD and KS respond to reduction or cessation of immunosuppressive therapy.

Since immunosuppressive drugs were first used in transplant recipients in the early 1960s, great progress has been made, particularly in the last decade, because of increased experience, better surgical techniques, better patient selection, and improvements in immunosuppressive drug therapy and in the ability to prevent and treat many types of infection. One complication of intense and/or prolonged immunosuppressive therapy is an increased risk of cancer. In this review we shall examine the most common neoplasms and indicate what measures may be used to prevent and treat them. An extensive literature on the subject has evolved over the last 29 years. This review is largely based on findings of the Cincinnati Transplant Tumor Registry (CTTR),[1-6] the only worldwide registry dealing with malignancies in transplant patients. It is supplemented by reports from smaller regional registries, individual transplant centres, small series of cases and, occasionally, individual cases.

1. Commonest Malignancies Encountered

Overall, a 3- to 4-fold increased incidence of cancer has been observed in transplant patients compared with age-matched controls in the general population,[7] but there was a markedly increased incidence of certain neoplasms.[1-6] By July 1998, the CTTR had accumulated information on 11 483 malignancies that developed in 10 787 patients.[5] The CTTR found no increase in the incidence of malignancies that are commonly observed in the general population (carcinomas of the lung, breast, prostate, colon and invasive uterine cervical carcinomas).[1-6] The most common neoplasms were cancers of the skin and lips (4305 patients), post-transplant lymphoproliferative disease (1931 patients), Kaposi's sarcoma (KS) [465 patients], renal carcinomas (409 patients), uterine cervical carcinomas (353 patients), anogenital carcinomas (279 patients), hepatobiliary carcinomas (187 patients) and various sarcomas, excluding KS (146 patients).

These findings were consistent with several epidemiological studies that showed the following increases: 4- to 21-fold increase in skin cancers,[7,8] 29-fold increase in lip carcinomas,[9] 28- to 49-fold increase in non-Hodgkin's lymphomas,[7] 400- to 500-fold increase in KS compared with controls of the same ethnic origin,[10] 100-fold increase in vulval and anal carcinomas,[9] 20- to 38-fold increase in hepatocellular carcinomas,[11] and a 14- to 16-fold increase in *in situ* uterine cervical carcinomas.[12,13]

1.1 Cancers of the Skin and Lips

Skin cancers were shown to be the most common tumours and comprised 38% of all malignancies.[2-4] They developed on sun exposed areas, mainly of the head and neck, and upper extremities,[2-4,8,14] particularly in light-skinned individuals with blue eyes and blond or red hair.[8] In patients transplanted after 40 years of age, most tumours occurred on the head, whereas in those transplanted at a younger age

lesions developed mainly on hands, forearms and chest.[14]

The incidence of skin cancer increased with the length of follow-up after transplantation, as shown by an Australian study[15] of nearly 7000 cadaveric renal allograft recipients who experienced a linear increase in the incidence of cutaneous malignancies that reached 66% at 24 years after transplantation. Similarly, a Dutch study[16] showed a 10% incidence of nonmelanoma skin cancers in renal transplant recipients at 10 years after transplantation that rose to 40% after 20 years. The time of appearance after transplantation was shorter in older individuals than in younger recipients.[14]

In transplant patients, skin cancers showed several unusual features compared with their counterparts in the general population. Basal cell carcinomas (BCCs) outnumber squamous cell carcinomas (SCCs) in the general population by 5 to 1, but the opposite happened in transplant recipients, in whom SCCs outnumbered BCCs by 1.8 to 1. SCC was estimated to occur at a frequency between 40 and 250 times higher than that in the general population, BCC 10 times higher[16] and malignant melanoma 5 times more commonly than that expected.[8] In the general population, SCCs occur mostly in people in their 60s and 70s, but the average age of transplant patients was 30 years younger.[17] In addition, the incidence of multiple skin cancers in the CTTR was remarkably high (43%) and, despite being a worldwide collection, was similar to that seen only in areas of copious sunlight.[2-4,6] Some patients each had more than 100 skin cancers. Furthermore, in a number of individuals, there was an apparently widespread skin abnormality with areas of unstable epithelium containing multifocal premalignant and malignant lesions.[8]

In the general population, skin cancers are responsible for only 1 to 2% of all cancer deaths, the great majority of which are from malignant melanoma. In contrast, SCCs were much more aggressive in transplant patients than in the general population and accounted for the majority of lymph node metastases and deaths from skin cancer.[2-4,6] In the CTTR, almost 6% of patients with skin cancers had lymph node metastases of which 73% arose from SCCs, 17% from malignant melanomas and the remainder mainly from Merkel's cell tumours. Similarly, almost 5% of patients died of skin cancers, of which 60% were from SCCs, 30% from malignant melanomas, 8% from Merkel's cell tumours and 2% from BCCs. In transplant patients with SCCs, the density of the peritumoural cellular infiltrate was less than in controls individuals, perhaps contributing to their increased metastatic potential.[14] Aggressive SCCs occurred particularly where there was heavy sun exposure (outdoor workers), in older individuals, in patients with multiple lesions, particularly located on the head, and with histologically thick tumours that involved the subcutaneous tissues.[14] Patients with skin cancer were also more likely to develop other more fulminant types of malignancy than were allograft recipients who did not have skin cancer.[8]

Several factors may have predisposed patients to the development of skin cancers. Apart from the immunosuppressed state, exposure to sunlight was of major importance. There was 4- to 7-fold increased risk in regions with limited sunshine exposure, but in areas with copious exposure the risk was increased almost 21-fold over the already high incidence seen in the local population.[2-4,6-8,14,15] Not only does ultraviolet light have a direct carcinogenic effect on the skin, but it also causes a local immunodeficiency by decreasing the number of epidermal Langerhans cells, possibly facilitating proliferation of human papillomaviruses.[14] However, exposure to sunlight was not the only factor involved. A surprisingly high incidence of SCCs was reported from several countries having relatively little sunlight. Their development may have been related to malignant change in papillomavirus-induced cutaneous warts, under the influence of immunosuppression, sunlight and possibly other factors.[2-4,6,18,19] For example, a British study showed that 59% of 291 renal allograft recipients developed cutaneous warts and 22% had nonmelanoma skin cancers.[19] Currently, there is considerable controversy about the role of papillomavirus in the aetiology of skin cancers in transplant recipients. For example, a study of p53

gene mutations showed an important role for sunlight in the development of post-transplant skin cancer, irrespective of the human papillomavirus status of the patients.[20]

Human leucocyte antigen (HLA) plays an important role in host defences against the development and spread of neoplasms, especially with virus-induced malignancies.[21,22] In renal transplant recipients, HLA-A11 may have protected against skin cancers, whereas HLA-B27 and HLA-DR7 were associated with an increased risk of these tumours.[21] An association between HLA-B mismatching and HLA homozygosity and the development of skin neoplasms reported in Dutch allograft recipients[23] could not be confirmed in a study of their Australian counterparts.[24]

Some studies suggested that azathioprine played a role in causing skin cancers. Higher concentrations of the metabolite 6-thioguanine were found in erythrocytes of transplant patients with skin cancers than in control individuals,[25] and one of the metabolites of azathioprine is an imidazole that may sensitise the skin to sunlight.[26] However, recent investigations have shown no relationship of skin cancer to any particular immunosuppressive agent.[27]

1.2 Lymphomas and Lymphoproliferations

Of the post-transplant lymphomas, clear cut entities such as Hodgkin's disease and plasmacytoma/myeloma were much less common in the CTTR than in the general population, comprising less than 3 and 4% of lymphomas, respectively, compared with 10 and 19%, respectively, in the general population.[2-4,6] As regards the great majority of lesions, much confusion has arisen about their nomenclature. Consequently, the nonspecific term post-transplant lymphoproliferative disease (PTLD) has been widely accepted. This covers a very wide spectrum of disorders, ranging from benign hyperplasias at one end to frankly malignant lymphomas at the other. The hyperplasias include infectious mononucleosis and plasma cell hyperplasia, while the neoplasias include polymorphic PTLD, monomorphic (lymphomatous) PTLD, myeloma/plasmacytoma and lymphomas with Hodgkin's disease-like features.[28,29] Hyperplastic PTLDs are polyclonal in origin, whereas all neoplastic PTLDs contain a monoclonal component that can be detected by sensitive assays.[28] Of the PTLDs in the CTTR that were studied immunologically, 86% were of B cell origin, 14% were of T cell origin and rare cases were null cell origin or were combined B and T cell lymphomas.[2-6]

Moreover, of those PTLDs in the CTTR, 53% involved multiple organs or sites, and 47% were confined to a single organ or site.[2-4,6,30,31] Whereas lymphomas in the general population frequently involve lymph nodes, 70% of PTLDs occurred in extranodal sites, of which the most common were the liver (25%), lungs (21%), CNS (21%), intestines (19%), kidneys (18%) and spleen (12%). In patients with CNS disease, the brain was usually involved and the lesions were frequently multicentric in distribution.[2-4,6,29,32] Spinal cord involvement was rare. Another notable feature was that in 53% of patients with CNS involvement the lesions were confined to this site, whereas in the general population cerebral lymphomas are frequently associated with lesions in other organs, and only 1% of lymphomas are confined to the CNS.[32]

A remarkable finding in the CTTR was the frequency of either macroscopic or microscopic involvement of the allograft, which was affected in 23% of patients with PTLD.[2-4,6,30] In 30% of these patients the PTLD was localised to the allograft. In some renal, cardiac or hepatic allograft recipients the lymphomatous infiltrate was misdiagnosed as rejection when biopsies, done because of graft dysfunction, were studied microscopically. This resulted in incorrect management as immunosuppressive therapy was intensified, whereas a major treatment of PTLD involves reduction of dosage.[2-4,6,33]

Several factors predispose patients to PTLD.[2-4,6] Approximately 90 to 95% of PTLDs are positive for Epstein-Barr virus (EBV),[25,34] including several T cell PTLDs. A major risk factor is seronegative status at the time of transplantation. In one study,[35] 11% of seronegative paediatric and 5% of seronegative adult recipients developed PTLD, whereas the

corresponding figures in their seropositive counterparts were 0 and 2%, respectively.

Intense immunosuppressive therapy is a major risk factor for development of PTLD.[2-4,6] Often 3, 4 or even 5 immunosuppressive agents are administered over a short time span.[30,31] Whenever a new agent is introduced there is a 'learning curve' while we determine appropriate administration, especially when it is used in combination with other immunosuppressive medications. An increased frequency of lymphomas was noted after the introduction of antilymphocyte globulin (ALG), then cyclosporin, then muromonab-CD3 (OKT-3) and, with the limited experience gained thus far, tacrolimus (FK-506) and mycophenolate mofetil.

Nonrenal allograft recipients (such as heart or lungs) are much more likely to develop PTLDs than renal recipients.[2-4,6,30,31] Heavy immunosuppressive therapy is often used in the former group to reverse rejection in order to save their lives, whereas with severe rejection of kidney allografts physicians can discontinue immunosuppression and return the patients to dialysis therapy. Thus, when neoplasms in nonrenal allograft recipients were compared with those in renal recipients in the CTTR, lymphomas comprised 45% in the former group compared with only 12% in the latter.[31] These findings were reinforced by reports showing that PTLD occurs in less than 1% of renal recipients but in 3% of heart, 3% of liver, 8% of lung and 19% of intestinal recipients.[28,29] The risk of PTLD in bone marrow recipients is less than 2% at 4 years after transplantation, but may reach levels as high as 24% in recipients of HLA-mismatched T cell-depleted marrow.[28]

The CTTR data demonstrated that paediatric organ allograft recipients are much more prone to develop PTLD than adults. When neoplasms in paediatric patients were compared with those in adults, PTLDs comprised 53% of tumours in the former group compared with 15% in the latter.[31] A major reason for this difference is that primary EBV infections are more common in childhood than in adults, and are likely to result in PTLD in immunosuppressed patients.[36,37] Furthermore, 61% of paediatric patients who developed PTLDs received nonrenal organ allografts and therefore more intense immunosuppressive therapy. Another reason why lymphomas are more common in paediatric recipients is that children have more lymphoid tissue that may undergo neoplastic change when subjected to the appropriate stimuli.

1.3 Kaposi's Sarcoma (KS)

Remarkably, the total number of cases of KS in the CTTR exceeded those of each of 2 common neoplasms in the general population, namely colon and breast carcinomas.[2-4,6,38,39] The disease was uncommon in paediatric transplant recipients,[40] comprising only 3% of the KS patients in the CTTR.[2-4,6,38,39] The male to female ratio was nearly 3 : 1, whereas it was as high as 17 : 1 in classical KS. Furthermore, the great majority of patients tested negative for human immunodeficiency virus.[38,39] Of 279 patients whose racial or ethnic origins were noted, the majority were of Arab, Black, Italian, Jewish or Greek ancestry.[38,39] Several studies reinforced these findings. KS occurred in 1.6% of 820 Italian renal transplant recipients who were followed for more than 6 months.[41] It was the most common malignancy in renal transplant recipients in Saudi Arabia, comprising 76% of 46 neoplasms in one report[42] and 87.5% of 16 cancers in another study,[43] and affected 4.7 and 5.3%,[42] respectively, of renal transplant recipients, whereas the incidence of KS was 0.2 to 0.38% in the general population of Saudi Arabia.

60% of patients in the CTTR had nonvisceral KS limited to the skin or oropharyngeal mucosa, and 40% had visceral disease affecting mainly the gastrointestinal tract, lungs and lymph nodes, but other organs were also involved.[38,39] The majority (98%) of patients with nonvisceral disease had skin lesions and 2% had involvement of the mouth or oropharynx. Diagnosis was more difficult in patients who presented without typical skin lesions. Thus, 27% of patients who had visceral disease had no skin involvement, but 3% had oral lesions that provided ready access for biopsy and diagnosis.[38,39]

A physician should suspect KS whenever a transplant patient, particularly one belonging to the ethnic groups described above, presents with reddish blue macules or plaques in the skin or oropharyngeal mucosa, or apparently infected granulomas that fail to heal.[2-4,6,38,39] If the diagnosis is confirmed, a thorough workup, including computerised axial tomography (CAT) scans of the chest and abdomen, and upper and lower gastrointestinal endoscopy, is necessary to determine whether there is any internal visceral involvement. Diagnostic confusion may occur when the initial presentation of KS is a diffuse pulmonary infiltrate.[44]

Apart from the immunosuppressed state, infection with one or more types of virus is at least a co-factor in the aetiology of KS.[38,39] Human herpes virus-8 (HHV-8) a new herpes virus also known as Kaposi's sarcoma-associated herpes virus, has been isolated from various patient populations with KS, including renal transplant recipients, indicating an important role for this virus in KS pathogenesis.[45,46] Study of viral gene expression suggests that most cells in KS lesions are latently infected, while lytic viral replication is probably restricted to a much smaller subpopulation of cells.[46] This finding may affect therapy as drugs currently used against herpes viruses primarily affect lytic virus replication and do not eliminate latent viral infections.[47]

1.4 Renal Carcinomas

The CTTR data showed that 24% of renal carcinomas were discovered incidentally, when patients were being investigated for other disorders, at the time of nephrectomy performed for hypertension or other reasons, during operation for some other disease, or at autopsy examination.[2-4,6,48]

Most malignancies in renal recipients occurred in their own diseased kidneys, although 10% appeared in renal allografts from 2 to 258 (average 75) months after transplantation. Of these tumours, 23% were diagnosed within 2 years of transplantation. It is possible that they may have been present in the allografts at the time of transplantation but were small enough to escape detection.[2-4,6,48]

Compared with most other post-transplant cancers, that presumably arose as complications of immunosuppressive therapy, many renal carcinomas were related to the underlying kidney disease in renal allograft recipients.[2-4,6,48] However, no explanation is available for the small number of carcinomas that occurred in nonrenal allograft recipients. Two predisposing causes were identified.[2-4,6,48] Analgesic nephropathy was the indication for transplantation in 8% of transplant patients with carcinomas of their own diseased kidneys. This disorder is known to cause neoplasms, mostly transitional cell carcinomas, in various parts of the urinary tract. This is borne out in the CTTR series in which 59% of patients with analgesia-related renal tumours had similar carcinomas elsewhere in the urinary tract.[2-4,6,48]

Another predisposing cause was acquired cystic disease (ACD) of the recipients' own kidneys. ACD occurs in 30 to 95% of patients receiving long term haemodialysis, and is complicated by renal adenocarcinoma, which occurs 30- to 40-fold more frequently than in the general population.[48] ACD tends to regress in the presence of a successfully functioning transplant, and theoretically the risk of developing carcinoma is also reduced. However, cases of persistence of ACD and development of renal cell carcinoma have been reported in patients with successfully functioning kidney allografts.[48] The exact incidence of ACD-related carcinomas in renal transplant recipients is not known.

1.5 Carcinomas of the Uterus

In contrast with cervical carcinomas, no increase was observed in the incidence of endometrial carcinomas. Uterine cervical carcinomas occurred in 10% of the women with post-transplant cancers. The risk of invasive uterine cervical carcinoma was not increased. *In situ* lesions comprised at least 70% of cases.[2-4,6] As 2 epidemiological studies suggest a 14- to 16-fold increased incidence of *in situ* cervical carcinoma,[12,13] the relatively small numbers of cases reported to the CTTR may indicate that many cases are being missed. To avoid this error, post-adolescent female organ transplant recipients should have regular pelvic examinations and cervical

smears.[2-4,6] An important risk factor for cervical cancer is infection with human papillomaviruses, especially types 16 and 18.

1.6 Anogenital Carcinomas

These include carcinomas of the vulva, perineum, scrotum, penis, perianal skin or anus.[2-4,6,49] Females outnumbered males by 2.6 : 1 compared with patients with most other post-transplant malignancies, in whom males outnumbered females by more than 2 : 1.

One-third of patients had *in situ* lesions.[2-4,6,49] A worrying finding is that patients with invasive lesions were much younger (average age 42 years) than their counterparts in the general population, whose average age is usually between 50 and 70 years. More than 40% of transplant patients with these malignancies gave a preceding history of condylomata acuminata, usually caused by human papilloma virus types 16 and 18. Female patients sometimes exhibited a 'field effect' with malignancy affecting not only the vulva, but also the vagina and/or uterine cervix.[2-4,6,49]

1.7 Hepatobiliary Tumours

The majority (73%) of hepatobiliary tumours in the CTTR were hepatocellular carcinomas. Many were preceded by hepatitis B infection.[2-4,6,11] Since hepatitis C screening became available increasing numbers of hepatomas, related to chronic hepatitis C infection, are being reported.

1.8 Sarcomas (Excluding KS)

The majority of sarcomas involved the soft tissues or visceral organs, whereas cartilage or bone involvement was uncommon.[2-4,6,38] The most common types were fibrous histiocytoma, leiomyosarcoma, fibrosarcoma, rhabdomyosarcoma, haemangiosarcoma and mesothelioma.

1.9 Other Cancers

The Nordic Transplant Registry[50] and the Australian and New Zealand Transplant Registry[15] have reported an increased incidence of a broad variety of other neoplasms in addition to those described above. These may represent regional variations in cancer incidence. However, some of the calculated increases are based on very small numbers of patients. Whether or not there is an increased incidence of other malignancies will require epidemiological studies of large numbers of transplant recipients.[5]

2. Immunosuppressive Agents and Cancer Development

Successful maintenance of prolonged allograft function requires continuous therapy with powerful immunosuppressive agents that impair lymphocyte function. In the pioneering years of transplantation, immunosuppressive therapy consisted of 2 agents, azathioprine (or occasionally cyclophosphamide) and prednisone, supplemented, at some centres, by a brief course of ALG or antithymocyte globulin. Since the early 1980s, cyclosporin was in large part responsible for the dramatic improvement in the results of transplantation. The immunosuppressive armamentarium was also broadened by the introduction of various monoclonal antilymphocyte antibody preparations (of which muromonab-CD3 is the most widely used) and mycophenolate mofetil. The introduction of these new agents caused changes in therapy so that 3, 4 or even 5 drugs were given to some patients over a short span of time. As mentioned in section 1.2, there is a 'learning curve' following the introduction of a new immunosuppressive agent, which is associated with an increased incidence of PTLD.

The evolution of the neoplasms described above does not appear to be related to the use of any particular immunosuppressive agent. Table I summarises the CTTR experience to date. For example, 2 recent studies compared the malignancies observed in patients treated with tacrolimus-based regimens and with cyclosporin-based regimens.[51,52] There was little difference in the types of tumours observed and in the tumour rate. Furthermore, they differed little from those reported in previous studies when cyclosporin-based regimens were compared with azathioprine-based regimens.[53] One

Table I. The most common immunosuppressive measures currently used (Cincinnati Transplant Tumor Registry data)[a]

Agent or procedure	No. of patients	% of patients
Prednisone	10 509	92
Azathioprine	9340	81
Cyclosporin	5763	50
Antilymphocyte globulin or antithymocyte globulin	3055	27
Monoclonal antilymphocyte antibodies (mostly muromonab-CD3)	954	8
Splenectomy	836	7
Local irradiation of the allograft	747	7
Cyclophosphamide	468	4
Actinomycin	201	2
Tacrolimus	125	1
Total body irradiation	124	1
Mycophenolate mofetil	46	0.1

a Accumulated from patients with 11 483 tumours.

must emphasise caution in comparing the neoplasms seen after the use of recently-introduced drugs, as they do not provide a complete picture of the spectrum of malignancies. Post-transplant neoplasms appear an average of 5 years after transplantation. The length of follow-up of many patients treated with mycophenolate mofetil or tacrolimus falls well short of this figure.

Instead of being related to any individual immunosuppressive agents or combinations of agents, cancer development is linked to the immunosuppressed state *per se* which, among other factors, makes transplant recipients prone to a variety of virus-related tumours. Similar malignancies occur in 2 other states of immunodeficiency in which immunosuppressive therapy is not used. In naturally occurring immunodeficiency states there is a 100-fold increased risk of cancers, of which the most common are lymphomas, which have similar characteristics to many PTLDs.[30] In AIDS, the risk of developing certain cancers is greatly increased, particularly KS, non-Hodgkin's lymphoma and uterine cervical carcinoma.[30]

3. Prevention of Malignancies

Every effort should be made to prevent post-transplant cancers.[2-4,6,54] The level of immunosuppressive therapy should be kept as low as is compatible with good allograft function. Renal transplant physicians have learned by bitter experience that it is hazardous to continue with intense immunosuppressive therapy in the presence of repeated or persistent rejection. Rather, they found it better to stop immunosuppressive therapy and return the patient to dialysis until he/she had recovered sufficiently to attempt another transplant procedure. In the case of liver or heart transplantation there are, as yet, no means available to provide long term artificial support if the allograft should fail and, consequently, the patient is given large doses of immunosuppression in an attempt to rescue a rejecting graft. Although surgeons try to perform retransplantation in patients with rejecting cardiac and hepatic allografts before they develop complications of heavy immunosuppression, the shortage of donors remains a major obstacle to this endeavour.

Whenever possible, attempts should be made to prevent virus infections.[54] The increased incidence of hepatocellular cancer in transplant patients, related to hepatitis B infection,[11] may be prevented by administration of hepatitis B vaccine to potential transplant candidates.

In order to prevent PTLD, physicians are seeking for early warning markers of the disease. In one study,[55] 10 of 88 adult patients developed monoclonal (IgG) gammopathies. However, these were transient in 6 and persistent in 4. Only 1 patient developed PTLD 8 months after the occurrence of serum protein abnormalities. In another study of 201 patients,[56] 57 (28%) developed a monoclonal serum IgM or manifested monoclonal urinary light chains and 7 patients (3.5%) developed PTLD. The

monoclonal protein occurred in 5 of 7 patients (71%) with PTLD and 52 of 194 patients (27%) who did not develop this disorder. Further experience is needed in determining the significance of monoclonal gammopathy in predicting PTLD, as the gammopathy is frequently transient, it may be caused by bacterial or viral infections and it may occur many months before development of PTLD. As an alternative and probably more reliable approach, some investigators suggest that high EBV loads in the peripheral blood may herald the development of PTLD.[57,58]

Prevention of PTLD entails avoidance of overimmunosuppression.[2-4,6,30,31] In particular, one should try to avoid the use of multiple immunosuppressive agents administered over a short time period, and prolonged or repeated courses of potent antilymphocyte antibody preparations. When courses of intense immunosuppressive therapy are necessary, many physicians use aciclovir or ganciclovir, or related antiviral agents as prophylaxis against EBV. On theoretical grounds they may not be effective, as they are virustatic rather than virucidal and act only on the linear form of the virus and not on the circular (latent) form that is important in PTLD development. There are no prospective randomised controlled studies to test the efficacy of prophylactic aciclovir or ganciclovir administration. However, a recent study[59] showed that ganciclovir or aciclovir given pre-emptively, during administration of antilymphocyte agents, reduced the incidence of PTLD to 1 in 198 consecutive recipients, compared with a historic control group in which 7 of 179 recipients developed this problem. Antiviral prophylaxis is especially important when transplanting organs from EBV-positive donors into EBV-negative recipients, most of whom are children. However, PTLD may occur despite prophylaxis[60] and antiviral therapy alone may not be sufficient to decrease the risk of PTLD in high risk EBV-seronegative lung allograft recipients.[61]

Currently, there is no effective drug prophylaxis against other potentially oncogenic viruses such as HHV-8 and papillomaviruses. As papillomavirus infections are sexually transmitted, patients should be advised regarding barrier methods of contraception.[12,54] All postadolescent females should undergo regular pelvic examinations and cervical smears. All premalignant lesions, such as condylomata acuminata or uterine cervical dysplasia, should be treated early to try to prevent progression to cancer.[54]

As sunlight exposure is important in skin cancer development patients must avoid excessive exposure, especially individuals with light complexions, who are particularly prone to develop this problem.[2-4,6,8,14,54] If the patient's occupation or hobbies require much time in the sunlight then he/she should wear a wide brimmed hat, sun visors and protective clothing. Alternatively, he/she should protect the skin by regular use of sunscreens that filter out harmful ultraviolet-B rays. Unfortunately, many patients such as farmers, sailors or construction workers have already experienced many years of sun exposure before becoming transplant candidates. After transplantation, patients must be examined regularly, particularly those who spend much time in the sunlight, and any premalignant skin lesions carefully observed or treated. Topical retinoids may be useful to treat solar keratoses and warts,[16] but whether or not they reduce the risk of skin cancer is not clear. Systemic retinoids have also been used in small numbers of renal transplant recipients with numerous skin lesions.[14,62] However, retinoids have adverse effects including mucocutaneous xerosis, hair loss, hepatic intolerance, skeletal abnormalities and hyperlipidaemia,[14] which may increase the risk of ischaemic heart disease in many organ transplant recipients.

Questions arise as to whether kidney transplant recipients should be routinely screened for the early development of carcinomas in their own diseased kidneys. In view of the fact that close to 450 000 kidney transplants have been performed to date and only a few hundred have developed renal carcinomas, it is not cost effective to routinely screen every kidney recipient by regular ultrasound examinations to look for ACD-related malignancies. However, repeated urine cytology and CAT or ultrasound examinations of the urinary tract are advisable to

detect early carcinomas in patients with analgesic nephropathy.[48,54] Some surgeons routinely practice pretransplant bilateral nephroureterectomies in these patients to avoid the risk of malignant change in these structures. However, bladder carcinoma can still develop in such individuals.

As the incidence of cancer increases with the length of follow-up,[2-4,6,15] it is essential that patients be seen at regular intervals to treat premalignant lesions or investigate any untoward symptoms. Repeated surveillance is particularly important in known high risk groups.[54] For example, liver allograft recipients, whose underlying disease was sclerosing cholangitis that occurs as a complication of chronic ulcerative colitis, should undergo regular colonoscopies to detect and treat suspicious areas before they evolve into colon carcinomas.[54,63]

The ultimate preventative measure would be to avoid using immunosuppressive agents. Much research is currently in progress to induce immunological tolerance directed only at the foreign antigens of the allograft, but which leaves the immune system as a whole intact. When this can be accomplished, cancer will no longer be a complication of organ transplantation.

4. Treatment of Malignancies

Many cancers are treated by standard surgical, radiotherapeutic or chemotherapeutic measures. Treatment of skin cancers usually involves excision, although cryosurgery is used by some dermatologists for superficial BCCs and keratoses.[2-4,6,14] At times, skin grafting may be necessary and resurfacing of the dorsal aspects of the hands may be needed in patients with multiple lesions in these areas.[14] Repeated surgical excisions and multiple cryotherapy sessions may lead to considerable scarring and disfigurement. Some dermatologists advocate reduction of immunosuppressive therapy in patients with multiple skin cancers, but no convincing results of such treatments have been reported, and patients run the risk of losing their allografts. Some dermatologists use retinoids to try to reduce the risk of multiple and recurrent skin cancers.[14,62]

Several options are available for the treatment of PTLD. Multimodality therapy is often used.[2-4,6,29,30] Localised disease may be successfully excised or treated with radiation therapy. A significant number of more extensive lesions have regressed, partially or completely, after reduction or cessation of immunosuppressive therapy.[2-4,6,28,30,31,33] In particular, all immunosuppression should be stopped except for a minimal dose of prednisone in recipients with widespread, extensive or potentially life-threatening PTLD, until all evidence of malignancy has disappeared. Allograft rejection may not occur or may evolve slowly in a chronic fashion, as many of these patients have been very heavily immunosuppressed and a long time may elapse before they regain immunocompetence. Nevertheless, the risk of rejection does exist. For example, in a series of 14 renal recipients whose PTLD was treated (among other methods) by reduction or cessation of immunosuppression, 8 of 12 survivors lost their allografts.[64] Once PTLD has regressed, immunosuppressive therapy should be resumed in small doses and then gradually increased to maintenance levels which, however, should be lower than those given before the appearance of PTLD.

Aciclovir or ganciclovir is often used to treat an associated EBV infection.[2-4,6,29,34,37] Interferon-α may be used for its antiviral and antineoplastic effects. However, it is an immunostimulant and may precipitate rejection in large doses.[65] Chemotherapy may be successfully used to treat widespread PTLD, particularly with ProMACE/CytaBOM (prednisone + methotrexate + doxorubicin + cyclophosphamide + etoposide + cytarabine + bleomycin + vincristine).[66] In one series,[67] administration of anti-B cell monoclonal antibodies caused complete remissions in 58% of patients but not in individuals who had CNS disease. However, PTLD resolved in 2 such recipients when the antibodies were administered into the CNS via an Ommaya reservoir. Anti-EBV cytotoxic T cells, obtained from the original donor, have been used successfully to treat donor-cell derived PTLDs in bone marrow allograft recipients.[68] In one case, use of third party HLA-matched T cells was effective against a CNS

PTLD.[69] Lymphokine activated killer cells derived from the patients' own peripheral blood mononuclear cells have been used as a form of cellular immunotherapy and have been successful in several cases.[70] Other treatments that have been used include administration of IgG and administration of anti-CD22 immunotoxin.[71]

Outcomes were studied in 1345 patients with PTLD in the CTTR.[2-6,30] Of these, 223 patients (17%) were not treated, and the malignancy was discovered at autopsy in 104 of them (47%). It is a matter of concern that so many patients died without treatment, either because the diagnosis was missed or was made too late for effective therapy to be started. No data regarding treatment were available in 61 (5%) other patients. Treatment was given to 1061 patients, of whom 399 (38%) had complete remissions. Of the 1345 patients, both treated and untreated, 474 (35%) died of PTLD, 216 (16%) died of other causes (but PTLD may have contributed to some of the deaths) and 655 patients (49%) are currently alive.

Many treatments used for PTLD are also applicable to KS, including excision, radiotherapy, reduction of immunosuppressive therapy, administration of interferon-α and chemotherapy.[38,39] In the CTTR study, 42% of patients with KS had complete remissions following various treatments, and 38% of these occurred after reduction or cessation of immunosuppressive therapy.[2-4,6,38,39] Patients with nonvisceral disease had a higher remission rate (53%) than those with visceral disease (27%). Similar favourable responses to reduction of immunosuppressive therapy were also reported by other authors.[39] However, this treatment does have a price, as 59% of renal recipients in whom treatment was successful lost their allografts and another 6% had impaired function.[38] Striking results were reported in one study,[43] in which 8 of 13 patients (61%) had complete remissions after reduction of immunosuppressive therapy, and 69% of the recipients did not lose their grafts, even after a follow-up of many months.

If KS is not diagnosed or treated soon enough, it has substantial mortality. In the CTTR study, 57% of patients with visceral disease died, in whom 72% of deaths were from KS *per se*.[38,39] In contrast, only 23% of patients with nonvisceral KS died, most commonly from infection, rejection or from both causes, but rarely from KS.

With regard to treatment of other cancers, *in situ* carcinomas of the uterine cervix respond well to simple hysterectomy, cervical conisation or cryotherapy. *In situ* carcinomas or small anogenital neoplasms are treated by local excision. Large lesions require extensive operations such as total vulvectomy and inguinal node dissection, or abdominoperineal resection. Carcinomas of the kidney are treated by radical nephrectomy. Hepatocellular carcinomas, if localised, are treated by partial hepatectomy. Sarcomas (other than KS) are treated by wide excision, supplemented if necessary by radiation therapy or chemotherapy.[38]

Questions often arise about reduction or cessation of immunosuppressive therapy. These measures are useful in some patients with PTLD or KS. Unfortunately, such therapy often appears to be of little value in the treatment of other malignancies.[2-4,6] One has heard occasional anecdotal reports of reduction of skin cancer recurrences following reduction or cessation of immunosuppressive therapy, but no hard facts have yet been published.

In patients requiring cytotoxic therapy of extensive or widespread cancers, we must remember that most agents depress the bone marrow.[2-4,6] Therefore, it is prudent to stop or reduce dosage of azathioprine, cyclophosphamide or mycophenolate mofetil during such treatment to avoid severe bone marrow depression. As most cytotoxic drugs have immunosuppressive adverse effects, satisfactory allograft function may persist for prolonged periods. Treatment with prednisone may be continued, as it is an important component of many cancer chemotherapy protocols. As many patients, particularly with PTLD, are already heavily immunosuppressed, chemotherapeutic agents should be used with caution as some patients have died of overwhelming infections following their use. Severe leukopenia may require treatment with granulocytes or macrophage growth-stimulating factor.

5. Conclusions

To reduce the problems of cancer to a minimum, transplant physicians and surgeons should be familiar with the types of malignancies that may occur in their patients. They must keep immunosuppressive therapy to the minimum compatible with good allograft function. In addition, they should adopt prophylactic measures against tumours after transplantation, vigorously treat any precancerous lesions and carefully follow patients after transplantation, looking for any untoward symptoms and signs that enable them to detect cancers early and, hopefully, at a curable stage.

Acknowledgements

The author wished to thank numerous colleagues, working in the transplant centres throughout the world, who have generously contributed data concerning their patients to the Cincinnati Transplant Tumor Registry.

References

1. Penn I, Hammond W, Brettschneider L, et al. Malignant lymphomas in transplantation patients. Transplant Proc 1969; 1: 106-12
2. Penn I. Why do immunosuppressed patients develop cancer? In: Pimentel E, editor. Critical reviews in oncogenesis. Boca Raton (FL): CRC Press, 1989: 27-52
3. Penn I. The problem of cancer in organ transplant recipients: an overview. Transplant Sci l994; 4: 23-32
4. Penn I. Malignancy after immunosuppressive therapy: how can the risk be reduced? Clin Immunother l995; 9: 207-18
5. Penn I. Posttransplant malignancies. Transplant Proc 1999; 31 (1-2): 1260-2
6. Penn I. De novo cancers in organ allograft recipients. Curr Opin Organ Transplant 1995; 3: 188-96
7. Kinlen LJ. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. Am J Med l985; 78 Suppl. 1A: 44-9
8. Sheil AGR. Skin cancer in renal transplant recipients. Transplant Sci 1994; 4: 42-5
9. Blohme I, Brynger H. Malignant disease in renal transplant patients. Transplantation l985; 39: 23-35
10. Harwood AR, Osoba D, Hofstader SL, et al. Kaposi's sarcoma in recipients of renal transplants. Am J Med l979; 67 (5): 759-65
11. Schröter GPJ, Weil III R, Penn I, et al. Hepatocellular carcinoma associated with chronic hepatitis B virus infection after kidney transplantation [letter]. Lancet 1982; 2: 38l-2
12. Sillman F, Stanek A, Sedlis A, et al. The relationship between human papillomavirus and lower genital intraepithelial neoplasia in immunosuppressed women. Am J Obstet Gynecol 1984; 150: 300-8
13. Porreco R, Penn I, Droegemueller W, et al. Gynecologic malignancies in immunosuppressed organ homograft recipients. Obstet Gynecol 1975; 45: 359-64
14. Euvrard S, Kanitakis J, Pouteil-Noble C, et al. Skin cancers in organ transplant recipients. Ann Transplant 1997; 2: 28-32
15. Sheil AGR, Disney APS, Mathew TH, et al. De novo malignancy emerges as a major cause of morbidity and late failure in renal transplantation. Transplant Proc 1993; 25: 1383-4
16. Hartevelt MM, Bouwes-Bavinck JN, Koote AM, et al. Incidence of skin cancer after renal transplantation in the Netherlands. Transplantation 1990; 49 (3): 506-9
17. Mullen DL, Silberberg SG, Penn I, et al. Squamous cell carcinoma of the skin and lip in renal homograft recipients. Cancer 1976; 37: 729-34
18. Barr BB, Benton EC, McLaren K, et al. Papillomavirus infection and skin cancer in renal allograft recipients. Lancet 1989; 2 (8656): 224-5
19. Glover MT, Niranjan N, Kwan JTC, et al. Non-melanoma skin cancer in renal transplant recipients: the extent of the problem and a strategy for management. Br J Plast Surg 1994; 47: 86-9
20. McGregor JM, Berkhout RJM, Rozycka M, et al. Mutations implicate sunlight in post-transplant skin cancer irrespective of human papillomavirus status. Oncogene 1997; 15: 1737-40
21. Festenstein H, Garrido F. MHC antigens and malignancy. Nature 1986; 322: 502-3
22. Dausset J, Colombani J, Hors J. Major histocompatibility complex and cancer, with special reference to human familial tumors (Hodgkin's disease and other malignancies). Cancer Surv 1982; 1: 119-47
23. Bouwes Bavinck JN. Epidemiological aspects of immunosuppression: role of exposure to sunlight and human papillomavirus on the development of skin cancer. Hum Exp Toxicol 1995; 14: 98
24. Bouwes Bavinck JN, Claas FJJ, Hardie D, et al. Relation between HLA Antigens and skin cancer in renal transplant recipients in Queensland, Australia. J Invest Dermatol 1997; 1008: 708-11
25. Lennard L, Thomas M, Harrington C, et al. Skin cancer in renal transplant patients is associated with increased concentrations of 6-thioguanine nucleotide in red blood cells. Br J Dermatol 1985; 113: 723-9
26. Hemmens VJ, Moore DE. Photochemical sensitization by azathioprine and its metabolites: II. Azathioprine and nitroimidazole metabolites. Photochem Photobiol 1986; 43 (3): 257-62
27. Bouwes Bavinck JN, Hardie D, Green A, et al. The risk of skin cancer in renal transplant recipients in Queensland, Australia. Transplantation 1996; 61: 715-21
28. Nalesnik MA. Clinicopathologic features of posttransplant lymphoproliferative disorders. Ann Transplant 1997; 2: 33-40
29. Nalesnik MA, Locker J, Jaffe R, et al. Experience with posttransplant lymphoproliferative disorder in solid organ transplant recipients. Clin Transplant 1992; 6: 249-52
30. Penn I. Immunosuppressive agents, immunodeficiency states and malignancy. In: Lieberman R, Mukherjee A, editors. Principles of drug development in transplantation and autoimmunity. Austin (TX): RG Landes, 1996: 93-102
31. Penn I. The role of immunosuppression in lymphoma formation. Springer Semin Immunopathol 1998; 20 (3-4): 343-55
32. Penn I, Porat G. Central nervous system lymphomas in organ allograft recipients. Transplantation 1995; 59: 240-4
33. Starzl TE, Nalesnik MA, Porter KA, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporine-steroid therapy. Lancet 1984; I: 583-7
34. Hanto DW. Classification of Epstein-Barr virus-associated posttransplant lymphoproliferative diseases: implications for understanding their pathogenesis and developing rational treatment strategies. Ann Rev Med 1995; 46: 381-94
35. Ho M, Jaffe R, Miller G, et al. The frequency of Epstein-Barr virus infection and associated lymphoproliferative syndrome after

transplantation and its manifestations in children. Transplantation 1988; 45: 719-27
36. Cao S, Cox K, Esquivel CO, et al. Posttransplant lymphoproliferative disorders and gastrointestinal manifestations of Epstein-Barr virus infection in children following liver transplantation. Transplantation 1998; 66: 851-6
37. Hanto DW, Birkenbach M, Frizzera G, et al. Confirmation of the heterogeneity of post-transplant Epstein-Barr virus-associated B cell proliferations by immunoglobulin gene rearrangement analyses. Transplantation 1989; 47: 458-64
38. Penn I. Sarcomas in organ allograft recipients. Transplantation 1995; 6O: 1485-91
39. Penn I. Kaposi's sarcoma in transplant recipients. Transplantation 1997; 64: 669-73
40. al-Sulaiman MH, Mousa DH, Rassoul Z, et al. Transplant-related Kaposi sarcoma in children. Nephrol Dial Transplant 1994; 9: 443-5
41. Montagnino G, Bencini PL, Tarantino A, et al. Clinical features and course of Kaposi's sarcoma in kidney transplant patients: report of 13 cases. Am J Nephrol 1994; 14: 12l-6
42. al-Sulaiman MH, Al-Khader AA. Kaposi's sarcoma in renal transplant recipients. Transplant Sci 1994; 4: 46-60
43. Qunibi W, Akhtar M, Sheth K, et al. Kaposi's sarcoma: the most common tumor after renal transplantation in Saudi Arabia. Am J Med 1988; 84: 225-32
44. Gunawardena KA, al-Hasani MK, Haleem A, et al. Pulmonary Kaposi's sarcoma in two recipients of renal transplants. Thorax 1988; 43: 653-6
45. Moore PS, Chang Y. Detection of herpes virus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. N Engl J Med 1995; 332: 1181-5
46. Kedda MA, Margolius L, Kew MC, et al. Kaposi's sarcoma-associated herpesvirus in Kaposi's sarcoma occurring in immunosuppressed renal transplant recipients. Clin Transplant 1996; 10: 429-31
47. Ensoli B, Barillari G, Gallo RC. Cytokines and growth factors in the pathogenesis of AIDS-associated Kaposi's sarcoma. Immunol Rev 1992; 127: 147-55
48. Penn I. Primary kidney tumors before and after renal transplantation. Transplantation 1995; 59: 480-5
49. Penn I. Cancers of the anogenital region in renal transplant recipients: analysis of 65 cases. Cancer 1986; 58: 611-6
50. Birkeland SA, Storm HH, Lamm LU, et al. Cancer risk after renal transplantation in the Nordic countries 1964-1986. Int J Cancer 1995; 60: 183-9
51. Wiesner RH. A long term comparison of tacrolimus (FK506) versus cyclosporine in liver transplantation: a report of the United States FK506 Study Group. Transplantation 1998; 66: 493-9
52. Jonas S, Rayes N, Neumann U, et al. De novo malignancies after liver transplantation using tacrolimus-based protocols or cyclosporine-based quadruple immunosuppression with an interleukin-2 receptor antibody or antithymocyte globulin. Cancer 1997; 80: 1141-50
53. Penn I. Cancers in cyclosporine-treated versus azathioprine-treated patients. Transplant Proc 1996; 28: 876-8
54. Penn I. Posttransplant malignancies: clinical preventative measures. In: Schmahl D, Penn I, editors. Cancers in organ transplant recipients. Berlin: Springer-Verlag, 1991: 157-60
55. Pham H, Lemoine A, Salvucci M, et al. Occurrence of gammopathies and lymphoproliferative disorders in liver transplant recipients randomized to tacrolimus (FK506)- or cyclosporine-based immunosuppression. Liver Transplant Surg 1998; 4: 146-51
56. Badley AD, Portela DF, Patel R, et al. Development of monoclonal gammopathy precedes the development of Epstein-Barr virus-induced post-transplant lymphoproliferative disorder. Liver Transplant Surg 1996; 2: 375-82
57. Rowe DT, Qu L, Reyes J, et al. Use of quantitative competitive PCR to measure Epstein-Barr virus genome load in the peripheral blood of pediatric transplant patients with lymphoproliferative disorders. J Clin Microbiol 1997; 35: 1612-5
58. Green M, Reyes J, Rowe D. New strategies in the prevention and management of Epstein-Barr virus infection and post-transplant lymphoproliferative disease following solid organ transplantation. Curr Opin Transplant 1998; 3: 143-7
59. McDiarmid SV, Jordon S, Kim GS, et al. Prevention and Preemptive therapy of posttransplant lymphoproliferative disease in pediatric liver recipients. Transplantation 1998; 66 (12): 1604-11
60. Kuo PC, Dafoe DC, Alfrey EJ, et al. Posttransplant lymphoproliferative disorder and Epstein-Barr virus prophylaxis. Transplantation 1995; 59: 135-8
61. Aris RM, Maia DM, Neuringer IP, et al. Posttransplantation lymphoproliferative disorder in the Epstein-Barr virus-naive lung transplant recipient. Am J Respir Crit Care Med 1996; 154: 1712-7
62. Bouwes Bavinck JN, Tieben LM, van der Woude FJ, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. J Clin Oncol 1995; 13: 1933-8
63. Fabia R, Levy MF, Testa G, et al. Colon carcinoma in patients undergoing liver transplantation. Am J Surg 1998; 176: 265-9
64. Hickey DP, Nalesnik MA, Vivas CA, et al. Renal retransplantation in patients who lost their allografts during management of previous posttransplant lymphoproliferative disease. Clin Transplant 1990 4: 187-90
65. Min AD. Does interferon precipitate rejection of liver allografts [editorial]? Hepatology 1995; 22: 1333-5
66. Swinnen LJ. Diagnosis and treatment of organ transplant-related lymphoma. Curr Opin Transplant 1998; 3: 90-5
67. Benkerrou M, Durandy A, Fischer A, et al. Therapy for transplant-related lymphoproliferative disease. Hematol Oncol Clin North Am 1993; 7: 467-75
68. Heslop HE, Rooney CM. Adoptive cellular immunotherapy for EBV lymphoproliferative disease. Immunol Rev 1997; 157: 217-22
69. Emanuel DJ, Lucas KG, Mallory Jr GB, et al. Treatment of Posttransplant lymphoproliferative disease in the central nervous system of a lung transplant recipient using allogeneic leukocytes. Transplantation 1997; 63: 1691-4
70. Nalesnik MA, Rao AS, Furukawa H, et al. Autologous lymphokine-activated killer cell therapy of Epstein-Barr virus-positive and -negative lymphoproliferative disorders arising in organ transplant recipients. Transplantation 1997; 63: 1200-5
71. Senderowicz AM, Vitetta E, Headlee D, et al. Complete sustained response of a refractory, post-transplantation, large B-cell lymphoma to an anti-CD22 immunotoxin. Ann Intern Med 1997; 126: 882-5

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