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Non-Hodgkin's lymphoma after kidney or heart transplantation: frequency of occurrence during the first posttransplant year

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Abstract The incidence of non-Hodgkin's lymphoma was analysed in over 70000 kidney transplant recipients and over 10000 heart, heart-lung or lung transplant recipients. An increased incidence of lymphomas during the first posttransplant year was observed in cadaver kidney recipients as compared to related kidney recipients, in thoracic organ recipients as compared to kidney recipients, in heart-lung recipients as compared to heart or lung recipients, in patients transplanted in North America as compared to patients transplanted in Europe, in patients receiving cyclosporine in combination with azathioprine as compared to patients with other immunosuppressive regimens, and in patients receiving ATG/ALG or monoclonal OKT3 for rejection prophylaxis.

Key words Lymphoma
Transplantation

Introduction

Organ transplant recipients require immunosuppressive treatment to prevent graft rejection and this has been associated with an increased risk of non-Hodgkin's lymphoma (NHL) [1–6]. The incidence rate of NHL has not been reliably estimated before. Previous studies have been based either on small numbers of patients with NHL or they have compared the frequency of NHL with that of other cancers without providing data on the absolute incidence. Moreover, these studies have usually been concerned with cumulative numbers of NHL without taking the time of follow-up into account. Naturally, the cumulative incidence increases with the lenght of follow-up; cumulative data are, therefore, not suitable for incidence rate comparisons among different patient populations. We analysed the incidence of NHL during the first posttransplant year in a large series of patients who had a complete 1-year follow-up.

Patients and methods

Kidney graft recipients transplanted between 1983 and 1991 and heart/heart-lung patients transplanted between 1985 and 1991 were studied. All patients had a 1-year posttransplant clinical follow-up. The analysis was restricted to centres participating in the Collaborative Transplant Study who provided written confirmation that the data on posttransplant NHL were complete. Date from more than 250 kidney and 100 heart transplant centres were included in the analysis. The following abbreviations are used for immunosuppressive drugs: CYA, cyclosporine A; STE, steroids; AZA, azathioprine; ATG, antithymocyte globulin; ALG, antilymphocyte globulin.

Results

Figure 1 illustrates the incidence rates of NHL per 100000 patients according to the type of organ transplanted. It is important to point out that different scales for incidence were used for kidney recipients and thoracic organ

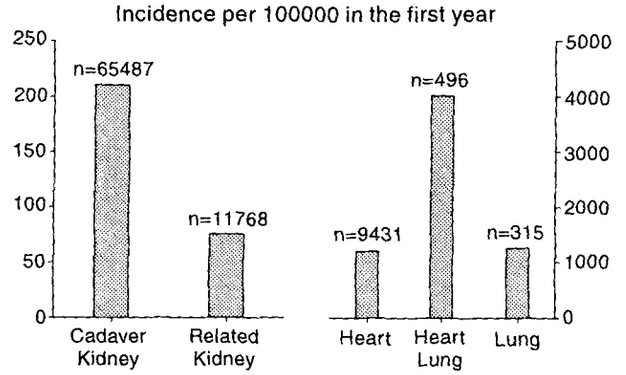

Fig. 1 Incidence of non-Hodgkin's lymphoma (NHL) during the first posttransplant year according to the type of transplant. Incidence per 100000 patients is plotted. Note that the scale for kidney transplants and thoracic organ transplants is different

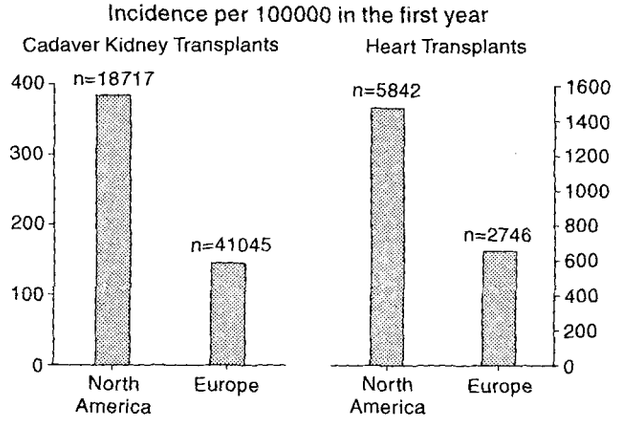

Fig. 2 Incidence of NHL per 100000 patients observed in North American and European transplant recipients. Both in kidney and heart transplant patients, the incidence of NHL was strikingly higher in North American recipients

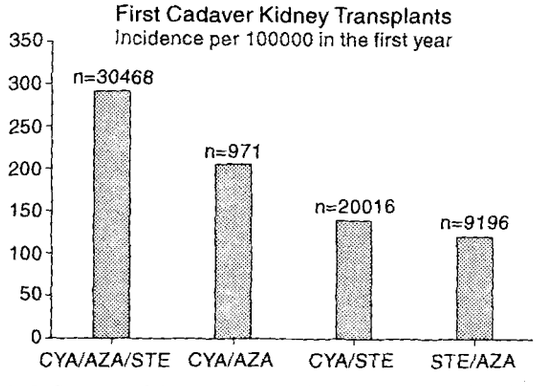

Fig. 3 Influence of immnosuppressive regimen on incidence of NHL during the first posttransplant year. Incidence per 100000 recipients of first cadaver kidney transplants is plotted (*CYA* cyclosporine A, *AZA* azathioprine, *STE* steroids)

recipients. The NHL rates in kidney transplant patients were much lower than those in thoracic organ recipients. Importantly, recipients of cadaver kidney transplants had a three times higher incidence of NHL (211/100000) than recipients of related donor kidney grafts (76/100000). Because recipients of related donor kidneys received smaller amounts of immunosuppressive drugs than cadaver transplant recipients, this difference in NHL incidence suggests that the strength of immunosuppression plays an important role in the development of posttransplant NHL. The strikingly higher rate of NHL in recipients of thoracic organ transplants further supports this assumption. It is known from the literature that heart transplant recipients receive higher doses of immunosuppressive drugs than kidney recipients [7]. Whether the excessive rate of 4032/100000 NHL in recipients of heart-lung transplants is a consequence of even stronger immunosuppression is not known. Because the number of patients studied ($n = 496$) was relatively small, the very high incidence of NHL in heart-lung recipients must be considered a preliminary result.

Both in cadaver kidney recipients and heart recipients, patients transplanted in North America exhibited a higher rate of NHL than patients transplanted in Europe (Fig. 2).

Detailed information on drug doses administered during the early posttransplant period was not available for analysis. However, maintenance doses reported at 1 year posttransplant were higher in North America than in Europe, and this may be an indicator of stronger immunosuppression in North America during the early posttransplant period also. At 1 year, kidney recipients transplanted in North America received a mean of 3.98 ± 0.07 (± 2 SE) mg/kg per day of CYA versus 3.86 ± 0.05 mg/kg per day in Europe ($P = 0.02$), and the corresponding values for AZA were 1.34 ± 0.02 versus 1.15 ± 0.02 ($P < 0.0001$). For heart transplant recipients, the 1-year maintenance doses for CYA were 4.54 ± 0.11 versus 4.52 ± 0.13 ($P =$ ns) and for AZA were 1.50 ± 0.03 versus 1.39 ± 0.05 ($P < 0.0001$) mg/kg per day for North America and Europe, respectively.

The influence of different immunosuppressive protocols in NHL incidence was evaluated in over 60000 cadaver kidney recipients. As shown in Fig. 3, triple drug therapy (CYA + STE + AZA) was associated with the highest NHL incidence. Importantly, the administration of CYA per se was not associated with an increased risk of NHL. Patients receiving CYA + STE had virtually the same incidence as patients receiving STE + AZA. However, the combination of CYA with AZA appeared to increase the risk.

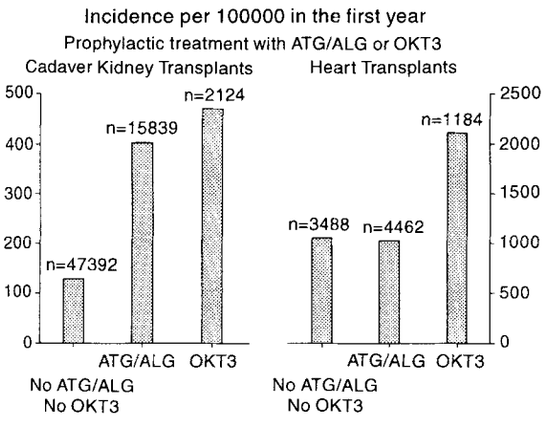

Fig. 4 Influence of prophylactic treatment with ATG/ALG or OKT3 on incidence of NHL during the first posttransplant year. Numbers of patients studied in each treatment group are indicated (*ATG* antithymocyte globulin, *ALG* antilymphocyte globulin)

The influence of prophylactic rejection treatment during the early posttransplant period with antithymocyte or antilymphocyte globulin (ATG/ALG) or the monoclonal anti-CD3 antibody OKT3 is illustrated in Fig. 4. In cadaver kidney recipients, patients receiving either ATG/ALG or OKT3 prophylaxis had a substantially higher rate of NHL than patients not receiving antibody prophylaxis. In heart transplant recipients, however, prophylaxis with ATG/ALG was not associated with an increased NHL incidence whereas prophylaxis with OKT3 was. Nevertheless, heart transplant patients who did not receive any antibody prophylaxis still had a much higher incidence of NHL than kidney transplant recipients with antibody prophylaxis (Fig. 4).

These data were subjected to statistical analysis using both Monte Carlo and logistic regression techniques [8, 9]. Considering all factors simultaneously, the incidence of NHL was significantly higher in heart transplant recipients than in kidney recipients ($P < 0.001$, relative risk 3.00), in North America than in Europe ($P < 0.001$, relative risk 2.12), in patients receiving prophylactic treatment with either ATG/ALG or OKT3 ($P < 0.005$, relative risk 1.80) and in patients receiving CYA together with AZA, irrespective of steroid use ($P = 0.02$, relative risk 1.47). Importantly, the incidence of NHL was not increased when CYA was administered without AZA.

Discussion

The large data material of the Collaborative Transplant Study allows meaningful incidence calculations of NHL after transplantation. Overall, the rate of NHL was approximately 20 times higher than in the normal population in kidney transplant recipients and approximately 120 times higher in heart transplant recipients [10, 11]. There were striking differences in the incidence rates observed in different patient populations. Type and strength of immunosuppressive treatment appeared to exert an important influence on the development of NHL. It has long been known that there is a thin line between immunosuppression sufficient for preventing threat of increasing the chance of NHL is a further important argument against oversuppression. There is circumstantial evidence that the higher rate of NHL observed in North America as compared to Europe may be a result of more aggressive immunosuppressive treatment. Published data, as well as data obtained by the Collaborative Transplant Study, indicate that graft survival results are not better in North America than in Europe. It would seem appropriate to attempt reductions in posttransplant immunosuppressive drug regimens to the minimum doses necessary for preventing rejection. Even in Europe, further reductions may be possible. In this context it will be interesting to evaluate whether transplants that are matched for the main histocomatibility (HLA) antigens can be sustained with lower immunosuppression. We would expect this to result in a lower incidence of posttransplant NHL.

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References

1. Penn I, Hammond W, Brettschneider L, Starzl TE (1969) Malignant lymphomas in transplantation patients. Transplant Proc 1: 106–112
2. Hoover R, Fraumeni JE Jr (1973) Risk of cancer in renal-transplant recipients. Lancet 2:55–57
3. Anderson JL, Fowles RE, Bieber CP, Stinson EB (1978) Idiopathic cardiomyopathy, age, and suppressor-cell dysfunction as risk determinants of lymphoma after cardiac transplantation. Lancet II:1174–1177
4. Cockburn ITR, Krupp P (1989) The risk of nepolasms in patients treated with cyclosporine A. J Autoimmun 2:723–731
5. Swinnen LJ, Constanzo-Nordin MR, Fisher S et al (1990) Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac transplant recipients. N Engl J Med 323:1723–1728

6. Cockfield SM, Preiksaitis J, Harvey E et al (1991) Is sequential use of ALG and OKT3 in renal transplants associated with an increased incidence of fulminant posttransplant lymphoproliferative disorder? Transplant Proc 23:1106–1107
7. Land W (1987) Optimal use of cyclosporine in clinical organ transplantation. Transplant Proc 19:130–135
8. Pregibon D (1981) Logistic regression diagnostics. Ann Statist 9:705–724
9. McCullagh P, Nelder JA (eds) (1989) Generalised linear models, 2nd edn. Chapman and Hall, London
10. Muir C, Waterhouse J, Mack T, Powell J, Whelan S (eds) (1987) Cancer incidence in five continents, vol V. International agency for research on cancer, Lyon
11. Jensen OM, Esteve J, Moller H, Renard H (1990) Cancer in the European Community and its member states. Eur J Cancer 26:1167–1256