POST-TRANSPLANTATION MALIGNANT TUMORS AND THE CHALLENGES OF IMMUNOSUPPRESSIVE THERAPY IN TRANSPLANTED PATIENS DEVELOPING LYMPHOMA.
MYCOPHENOLIC ACID – A POSSIBILITY.

Doctoral theses

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Introduction

Malignant tumors occur more frequently in organ-transplanted patients than in non-transplanted individuals. The pattern of post-transplant tumors are different from that of the general population. The risk is 2-4-fold, and in some cases it can be even 100-fold, compared to the normal population. The primary factor in tumor development is immunosuppression, and the risk of tumor development is directly proportional to the time period of the immunosuppressed state. Cumulative tumor incidence can reach 20% after 10 years and 30-40% after 20 years following organ transplantation. Posttransplant malignancies are characterized by an unfavorable prognosis and poor response to oncological treatment. Tumors following organ transplantation are becoming one of the major factors determining the fate and survival of patients, due to their increasing frequency and poor prognosis. Cardiovascular factors, until now the leading causes of patient mortality, are being caught up by tumors in several transplantation centers. Taken together, we have to face the increasingly serious problematic of posttransplantation tumors. Like the tumors of the general population, posttransplantation tumors show geographical characteristics in different parts of the world as well. In order to efficiently find solutions, we have to know the special characteristics of our own region, in addition to the data presented in the literature.

Lymphomas are the most important tumors following organ transplantation, due to their frequency and poor prognosis. They are the second most common tumors in adults (after skin cancer), and the most frequent tumors in childhood. Lymphoma risk is 20-120 fold after transplantation compared to the non-transplanted population. It is mainly of B-cell origin and associated with Epstein-Barr virus. The disease responds poorly to therapy, and 5-year survival is 30%. Treatment options are similar to those of the ”traditional” lymphomas of the non-organ transplanted population. An important issue in therapy is immunosuppression. When beginning the therapy, it is highly recommended to reduce the dosage or omit the drug. However, patients in remission need some type of immunosuppression in order to protect the transplanted organ. The ideal immunosuppressive compound would prevent graft rejection, and at the same time, would not interfere with oncological

treatment and would not increase the risk of relapse. The literature recommends rapamycin, based on its anti-proliferative effects. However, rapamycin in itself may not be sufficient, and it has its own side effects and counter-indications. Thus, other, alternative immunosuppressive drugs are needed for this situation; however, specific recommendations are lacking, and the immunosuppression of organ transplanted patients with lymphoma is still an open question. While seeking a solution to this problem, the focus of our interest has turned to mycophenolic acid, an anti-proliferative and anti-metabolite compound, which exerts it immunosuppressive effect by inhibiting *de novo* purin nucleotide synthesis in activated lymphocytes. If mycophenolic acid were proved to have similar effects in lymphoma cells, it could be used in the treatment of lymphomas in transplanted patients, and of the ”traditional” lymphomas of the general population as well.

Aim of the study

1. To collect and analyze data about malignant tumors following kidney transplantation in Hungary, and drawing appropriate conclusions regarding the management of these conditions – based on nearly 2900 kidney transplantations performed during the last 33 years in Budapest.
2. To explore the anti-proliferative effects of mycophenolic acid on human B-cell non-Hodgkin lymphomas – both *in vitro* and in animal models –, as a possible solution for the problem of immunosuppression of transplanted patients with lymphoma.

Methods

1. **Patients and methods – data analysis of tumors following kidney transplantation**

Between 1973 and 2007, 2852 renal transplantations were performed in the Kidney Transplant Program of Semmelweis University, Budapest, Hungary: 2535 primary, 294 secondary and 23 tertiary transplantations. All our transplanted patients were followed at our out-patient care unit as long as their transplanted kidney functioned. In case of complication they were admitted to our

department. The patients' data and posttransplantation complications, including malignancies, are registered in our data base. Our retrospective analysis was based on the data of this register. In January 2007, 1300 patients had a functioning graft and were regularly followed, while 2% were lost to follow-up. The mean follow-up time of tumor patients was 94.11 months. Malignancies were found in 188 transplanted patients. The male/female ratio was 2.19:1 (129/59). The mean age of patients was 53.1±10.1 years, men were significantly older than women (54.3±10.0 vs. 51.4±9.9 years; p=0.017). Tumors occurred after primary and secondary transplants in 170 and 18 cases, respectively. Mean HLA mismatch was 2.83 ±0.6. The incidence of malignancies of the renal transplanted patients and of the Hungarian general population was compared according to data of the Hungarian National Cancer Registry. Patients with malignancies were classified into four groups based on the type of immunosuppressive therapy: group I, azathioprine + prednisone (n=16), 8.5%; group II, cyclosporine + prednisone (n=111), 59.0%; group III, cyclosporine + mycophenolate mofetil + prednisone (n=50), 26.6%; group IV, tacrolimus + mycophenolate mofetil + prednisone (n=11), 5.9%. The Hungarian kidney transplantation program started in 1973. The first group received the initial prednisone + azathioprine conventional therapy. Cyclosporine + prednisone combination was introduced in 1984 (group II). Mycophenolate mofetil was added to the previous protocol (group III) in 1997, and the administration of tacrolimus was initiated in 2000 (group IV). Induction therapy (OKT3, ATG, anti-CD25 (IL-2 receptor) monoclonal antibody) was used only in secondary transplant patients. Fisher's exact t-test was used for comparisons between individual groups and analysis of variance (ANOVA) was used to calculate mean and standard deviations. Survival rates were calculated with the Kaplan-Meier method, and log-rank test was used to compare survival rates among these groups. $p<0.05$ was considered statistically significant. Statistical analysis was performed with SAS software version 8.2.

2. Methods – *in vitro* and *in vivo* effects of mycophenolic acid on human B-cell non-Hodgkin lymphomas

Cell culture systems

Experiments were performed on **HT58** (EBV− cell line established in our laboratory), **BL41** (EBV−), **BL41/95** (EBV+) human Burkitt lymphoma cell lines, **MED-B1** DLBCL and **U266** human myeloma cell lines. Cells were cultured in RPMI-1640 with 10% fetal bovine serum and penicillin-streptomycin (Sigma, St Louis, MO, USA). Cells were treated for 0–72 h with mycophenolic acid (MPA, Sigma) (0.05–50 μM) and guanosine (Sigma) (0.1–100 μM) in 24-well plates or 25 cm^2 flasks at a density of $1–2\times10^5$ cells/ml. Experiments were done in triplicates, and three independent experiments were performed for each measurement.

Flow cytometry: cell cycle, apoptosis and mitochondrial membrane depolarization

For apoptosis detection cells were fixed in 70% ethanol (−20 ◦C) followed by alkalic extraction (200mMNa_2HPO_4, pH7.4 and 100 μg/ml RNase (Sigma)) and ethidium-bromide staining (10 μg/ml, Sigma). Flow cytometric evaluation of cell cycle and apoptotis was performed on a FACScan flow cytometer (BD Biosciences, Erembodegem, Belgium). Data was analyzed withWinList software (Verity Software House, Topsman, ME, USA). To detect mitochondrial membrane depolarization, 5×10^5 cells were incubated with DiOC6 (10 nM, Molecular Probes) and propidium iodide (5 μg/ml) for 15 min and changes in fluorescence were measured by flow cytometry at 530–620 nm.

Caspase2 and caspase3 activation assay

Cells (0.5×10^6 cells/ml) were suspended in caspase buffer solution (50mM HEPES, 100mM NaCl, 0.1% (w/v) CHAPS, 10% (w/v) sucrose, 10mM DTT, Sigma). For caspase2 activation assays 0-200-1000nM zVAD-fmk (Sigma) caspase inhibitor was added to the buffer to eliminate nonspecific caspase effects on the substrate (Ac-VDVAD-afc). Cells were lysed (0.1% Triton X-100) and the released amc and afc (from Ac-DEVD-amc (caspase3) or Ac-VDVADafc (caspase2) substrates (50_M, Bachem, Weil, Germany) were recorded on a fluorescence plate reader (Fluoroscan Ascent

Fluorimeter, Thermo Electron Corp., Waltham, MA, USA) for 15–20 min at 390/460 nm and 400/505 nm, respectively. Results were evaluated by Microcal Origin Software by the detection of staurosporin (6 h, 1 μM; Sigma) treatment induced caspase2 activity in HL60 cells in parallel measurements.

Xenograft tumors

Xenograft tumors were established in immunocompromised/SCID mice. 2×10^7 tumor cells were injected subcutaneously (s.c.) into the back region of 8–10 week old SCID (20–23 g) mice. Palpable s.c. tumors formed after 10–13 days in each control mouse. For *in vivo* experiments, mycophenolate mofetil (MMF) (Cellcept 250 mg capsule, Roche, Basel, Switzerland) was administered by gavage at 100 mg/kg body weight in 200 μl 0.9% saline once a day (n = 10), according to previously described and tested doses. Control groups were treated with 200 μl 0.9% saline by gavage once a day (n = 10). Body weight and tumor diameters were measured. Tumor volume was calculated as follows: $\pi/6\times(2\times\text{shorter diameter} + \text{longer diameter})/3)^3$. Tumor weight was measured in euthanized animals at the end of experiments. Different strategies were used to evaluate the effect of MMF *in vivo*: MMF treatment was initiated (a) 24 h after the injection of tumor cells, or (b) 13 days after the injection (when tumors were palpable). All procedures were approved by the Institutional Review Board (licence no.: 399/003/2005).

Immunohistochemistry

Apoptotic and proliferative activities of lymphoma cells were also determined in xenograft tissue specimens. The removed tumors were formalin fixed and paraffin embedded. BrdU labeled tumors (BrdU (100 mg/kg) (Sigma) was injected intraperitoneally 1 h before the termination of *in vivo* experiments) were fixed in 60% ethanol + 10% formaldehyde. Immunostainings were performed with monoclonal anti-Ki67 (Dako, Glostrup, Denmark), anti-cleaved caspase3 (Cell Signaling, Beverly, MA, USA) and anti-BrdU (BD) primary antibodies using a streptavidin-biotin peroxidase system (Dako, Glostrup, Denmark) in a Ventana ES automat (Ventana Medical Systems, Inc., Cedex, France). The number and proportion of mitotic and apoptotic as well as Ki67, cleaved caspase3 and BrdU

positive tumor cells were counted in high-power fields (X400) of H&E or IHC stained sections by two independent investigators. Only the areas of tumor tissue (1000 cells) were enumerated, necrotic parts and stromal elements were disregarded.

Isolation and re-culture of isolated tumor cells

Ficoll (Histopaque 1077, Sigma) gradient separeted mononuclear cells from manually disrupted tissues (removed tumors) were labelled with anti-human CD19-MACS microbeads (Miltenyi Biotec, Bergisch Gladbach, Germany) and subsequently separated on MACS Columns (Miltenyi). The isolated tumor cells were re-cultured for 2 weeks. MPA sensitivity/resistance was determined *in vitro* as described above.

Statistical analysis

Descriptive statistics (*n*, mean and S.D.) was applied for data analysis. Student's *t*-test was applied for evaluating significance, a *p*-value of <0.05 was considered statistically significant. Statistical analysis of data was performed using SAS version 8.2 forWindows (SAS Institute Inc., Cary, NC, USA).

Results

1. Analysis of malignant tumors following kidney transplantation

Posttransplantation malignancies

During the last 33 years we detected 193 malignant diseases in 188 out of 2535 patients, indicating a tumor incidence of 7.6%. The most frequent tumors were: skin cancer (n=51), renal cancer (n=26), lung cancer (n=15), Kaposi's sarcoma (n=12), breast cancer (n=12), non-Hodgkin lymphoma (n=10), hepatic cancer (n=7), thyroid cancer (n=6), colorectal cancer (n=6) and malignant melanoma (n=6). Malignant tumors observed in the first four years following renal transplantation were compared to the data registered between 2001 and 2004 in the National Cancer Registry. Our data show that of the common malignancies only skin- and gastric cancers (2.58- and 1.61-fold, respectively) displayed a higher incidence than in the general population, whereas the incidence of

lung-, colorectal-, oral- and prostate cancers was lower than in the general population (>30%). On the other hand, the incidence of lymphomas was only slightly higher, which can be explained by the fact that, surprisingly, lymphomas occurred 5 to 10 years after transplantation in our patients. The incidence of Kaposi sarcoma (6.2%) was also high in the transplanted patient's population. The frequency of hepatic-, renal- and thyroid cancers was 3.25-, 6.77- and 8.95-fold higher, respectively, compared to the nontransplanted population.

Comparison of tumor patients in the four groups with different immunosuppressive regimens

ANOVA analysis of the data showed a significant difference in the mean age ($p<0.003$) and the time interval between transplantation and tumor detection ($p<0.0001$) in all groups. The mean age of patients increased over time both with regard to the time of transplantation and also the time of tumor detection. At the beginning of the Hungarian transplant program only young patients were transplanted (the mean age was 37.1±7.4 years, group I). Group IV included patients transplanted in and after 2000, with a significantly higher mean age at the time of transplantation (56.0±8.3 years). We also observed a shortening of the time between the onset of the tumor and transplantation. Analysis of the data revealed a significant correlation with the changing type of immunosuppression ($p<0.0001$) but showed no significant correlation with increasing age ($p<0.14$).

Time elapsed between transplantation and the appearance of tumors

The mean time from transplantation to tumor detection was 58.5±44.8 months; 11.4% (n=22) were detected within 6 months, 20.2% (n=39) within the first year, 35.2% (n=68) within two years, 93.3% within ten years (n=180) and 6.7% (n=13) after 10 years. In the case of more frequent tumors the ratios of detection within the first year were: cancer of the native kidney 38.46%, lung cancer 20.0%, breast cancer 33.4%, Kaposi's sarcoma 58.3%, lymphoma 0% (!). In the four immunosuppressive groups mentioned above the percentage of tumors that were diagnosed within the first year were 12.5% (2/16) in group I, 18.9% (21/111) in group II, 22.0% (11/50) in group III and 45.5% (5/11) in group IV.

Cause and time of death

Ninety-two out of 188 patients (48.9%) died during the observation period. Their mean age was 54.8±10.4 years at the time of death. Mean survival time after the diagnosis of the tumor was 25.8±39.4 months in the deceased population; 36.9% (n=34) died within 6 months, 55.4% (n=51) within 12 months, 70.6% (n=65) within 24 months and 84.7% (n=78) within 60 months. The cause of death was tumor progression in 32.6% (n=30), while 30.4% (n=28) died of infection (pneumonia and sepsis). Cardiac complications, lung embolism, cerebrovascular accidents, liver cirrhosis, hepatic failure, acute pancreatitis and tuberculosis were the causes of death in the remaining 37% (n=34). The mean follow-up time of the 96 patients who were alive at the end of this study was 65.7±46.6 months.

Patient survival data

The cumulative survival rate of the 188 tumor patients according to the Kaplan-Meier method was 69.5% at 1 year, 61.8% at 2 years, 57.3% at 3 years and 52% at 5 years. Survival was best in the skin cancer subgroup: 90.2% at 1 year and 75.9% at 5 years. The prognosis of other types of cancer was much worse: 59.2% at 1 year and 38% at 5 years. Overall survival was 81.3% at 1 year and 60.4% at 5 years in women, and 63.8% at 1 year and 46.3% at 5 years in men. Survival rate was significantly higher in women (p =0.0138).

2. *In vitro* and *in vivo* effects of mycophenolic acid – an immunosuppressive drug – on human B-cell non-Hodgkin lymphomas

MPA has antiproliferative and proapoptotic effects in vitro

MPA had antiproliferative and proapoptotic effects in all examined cell lines in a time- and dose-dependent fashion. Accumulation of cells in G1 phase was observed after 24 h MPA treatment, followed by G2 block at 64 h and apoptotic/cell death catastrophe at 72 h, there was no difference in the sensitivity of EBV+/− Burkitt lymphoma cell lines. MPA also induced apoptosis and inhibited proliferation in U266 myeloma cells (percentage of apoptotic cells: control: 9±2%, 5 μM MPA: 65±4% at 72 h). Inhibition of proliferation was more pronounced in MED-B1

DLBCL cells – cells were arrested before progressing to G2 phase at 96 h –, and a longer time period (96 h) was required for apoptosis induction (control: 2±0.5%, 5 μMPA: 21±1%). Guanosin (0,1-100μM) could not abolish the apoptotic and antiproliferative effect of MPA (5μM) *in vitro*, since the salvage mechanism does not work in lymphocytes and lymphoma cells.

MPA induced apoptosis involves mitochondrial depolarization and caspase3 activation

Mitochondrial depolarization coincided with the start of induced apoptosis at 48 h. The role of mitochondria was also confirmed by a concomitant decrease of bcl-2 protein. Caspase3 activation was determined with a fluorimetric caspase activation assay after mitochondrial depolarization, at 40 h. Caspase2 activity was not detectable, contrary to what was described previously.

MMF suppresses tumor growth in vivo

MMF – a derivative of MPA – treatment from the first day after tumor injection resulted in growth delay in HT58, BL41 and BL41/95 xenografts. Average tumor weight was significantly lower (15–24% of the control) in the treated group, and the difference in calculated tumor volume was also significant. Notably, there was a dramatic increase in tumor volume after day 25 in control animals, which was not observed in MMF-treated mice. When MMF treatment was initiated after tumor formation (day 10–13), the growth of already developed tumors was suppressed by MMF treatment as well. H&E and immunohistochemical stainings (Anti-BrdU, Ki67) of sections from removed, formalin fixed and paraffin embedded tumors showed significant inhibition of cell proliferation in MMF treated tumors. Evaluation of active caspase3 in parallel with H&E stainings showed that MMF induced apoptosis in xenografted tumors *in vivo*. After a 28 day MMF treatment, lymphoma cells were isolated from s.c. tumors of treated and control mice and re-cultured *in vitro*. The "new" cell lines were treated with MPA *in vitro*.MPA induced 50–60% apoptosis at 72 h after treatment in all samples, indicating that HT58, BL41 and BL41/95 lymphoma xenografts retained MMF/MPA sensitivity after *in vivo* MMF treatment.

Conclusions

1. Conclusions based on the data analysis of malignant tumors following kidney transplantation

1. We showed that malignant tumors occur more frequently in our kidney-transplanted patients than in the non-transplanted Hungarian population. Our results are in line with literature data.

2. We analyzed and compared for the first time the incidence of frequent malignant tumors in the Hungarian kidney-transplanted and non-transplanted population, and published our results in international, peer-reviewed journals.

3. From among the frequent tumors of the Hungarian population, only skin and gastric cancer showed a – moderately – higher incidence in kidney-transplanted patients, whereas the incidence of lung, colorectal, breast, oral and prostate cancer was lower.

4. The mean time between transplantation and the manifestation of tumors decreased in the chronologically consecutive patient groups, which received different immunosuppressive regimens. A possible explanation is the difference in immunosuppression, however, conclusive evidence is still lacking due to the different number of cases and follow-up time periods.

5. Nearly 20% of the tumors were observed within the first year following kidney transplantation. This may be of importance because early manifesting tumors may be unrecognizable or undiagnosed, but present in patients at the time of transplantation.

6. The mean age of our patients at the time of kidney transplantation and at tumor diagnosis has been increasing since 1973. The higher age of patients with renal diseases increases the risk of tumor development.

7. We determined for the first time the cumulative and tumor specific 1- and 5-year survival rates of kidney transplanted tumor patients in Hungary, and published our results in international peer-reviewed journals. Tumors with the most favorable prognosis were skin and thyroid cancer, whereas Kaposi’s sarcoma, lung and hepatic

cancer and non-Hodgkin lymphomas had the worst prognosis. Survival was better among women, which may be due to the lower incidence of poor prognosis tumors among them.

8. Given the higher tumor risk due to chronic renal insufficiency and the increasing age of patients with renal disease, as well as the incidence of early tumors following kidney transplantation, we think that regular oncological screening of prospective recipients on the waiting list is essential to prevent transplantation when a tumor is present.

9. We made a recommendation for the regular oncological screening of prospective kidney recipients and kidney transplanted patients, which was presented at conferences and in national and international journals.

10. Based on our results, our aim is to decrease the tumor risk following organ transplantation. Patient information to prevent carcinogenic noxas, and regular oncological screening for the early discovery and treatment of precancerous conditions and tumors are of utmost importance; in addition, the risk of chronic immunosuppression should be decreased by utilizing lower doses of drugs and compounds which still protect the graft but have an oncologically more favorable effect.

2. **Conclusions based on the studies of mycophenolic acid – an immunosuppressive drug – in in vitro and in vivo human non-Hodgkin lymphoma models**

1. We showed and published for the first time that mycophenolic acid inhibits the proliferation of certain lymphoma cells *in vitro*.

2. We showed and published for the first time that mycophenolic acid induces apoptosis in lymphoma cells *in vitro*.

3. We showed and published for the first time that mycophenolic acid induces apoptosis in lymphoma cells by activating the intrinsic (mitochondrial) pathway.

4. We showed and published that the presence of guanosine does not abolish the anti-proliferative and pro-apoptotic effects of

mycophenolic acid in lymphoma cells, i.e. lymphoma cells – similarly to lymphocytes – lack the salvage mechanism in guanine nucleotide synthesis.

5. We showed and published that mycophenolic acid significantly inhibits lymphoma growth *in vivo*. It is also effective when treatment is initiated when tumors are already palpable.

6. We showed and published for the first time that mycophenolic acid induces apoptosis in lymphoma cells *in vivo* as well.

7. We showed and published for the first time that *in vitro* lymphoma cells derived from *in vivo* xenograft tumors do not develop resistance to mycophenolic acid.

8. Based on the anti-proliferative and pro-apoptotic properties of mycophenolic acid in the examined human B-cell non-Hodgkin lymphomas, it may be recommended for the immunosuppression and the therapy of transplanted patients developing lymphoma, as well as the treatment of ”traditional” lymphomas of the non-transplanted population.

List of publications

Publications supporting the doctoral theses

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