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Anti-CD20 antibody (rituximab) administration in patients with late-occurring lymphomas after solid organ transplant

GIANPIETRO DOTTI,* ALESSANDRO RAMBALDI,* ROBERTO FIOCCHI,° TERESIO MOTTA,# GIULIANO TORRE,@ PIERA VIERO,* BRUNO GRIDELLI,@ TIZIANO BARBUI*
Divisions of *Hematology, °Heart Surgery, #Pathology, @Liver Transplant Center, Ospedali Riuniti di Bergamo, Italy

Correspondence: Alessandro Rambaldi, M.D., Division of Hematology, Ospedali Riuniti di Bergamo, Largo Barozzi 1, 24128 Bergamo, Italy. Phone: international +39-035-266808 - Fax: international +39-035-266147 - E-mail: arambaldi@ospedaliriuniti.bergamo.it

Background and Objectives. Aggressive diffuse large cell non-Hodgkin's lymphoma (DLCL) occurring late after a solid organ transplant fails to regress after discontinuation of immunosuppression. Moreover, chemotherapy treatment is associated with a high mortality rate due to severe toxicity. Since the majority of post-transplant lymphoproliferative disorders derive from B-lineage lymphocytes, the administration of anti-B monoclonal antibodies represents a rational therapeutic option.

Design and Methods. Five patients who developed CD20-positive DLCL more than two years after heart or liver transplantation were treated with a weekly chemotherapy program (2 patients), radiotherapy (2 patients) and surgery (1 patient) followed by a minimum of 4 intravenous doses of rituximab (375 mg/m^2).

Results. A favorable clinical outcome was observed in three patients in whom surgery or radiotherapy had produced significant tumor debulking. Only a partial clinical effect was documented in the two patients with advanced clinical stage disease.

Interpretation and Conclusions. Rituximab can be safely administered to patients with aggressive CD20-positive DLCL occurring late after a solid organ transplant. However, a positive clinical outcome may be expected only in patients in whom surgery or radiotherapy has achieved significant regression of tumor burden.

Key words: solid organ transplant, allogeneic bone marrow transplant, immunosuppression, PTLD, rituximab, immunotherapy

Post-transplant lymphoproliferative disorders (PTLD) are polyclonal or monoclonal lymphoproliferation mediated by the Epstein-Barr virus (EBV) occurring in 1% to 10% of patients within the first or second year after solid organ transplant (SOT) or allogeneic bone marrow transplant (allo-BMT).[1,2] However, patients undergoing long-term immunosuppression treatment to prevent graft rejection maintain a higher risk of developing lymphomas compared to the general population.[2] These late-occurring PTLD have been recently characterized.[3,4] They differ significantly from early PTLD since they are invariably monoclonal proliferation, often negative for the EBV genome and sometimes associated with non-random genetic lesions.[3,4]

There is neither a uniform nor a standard approach for the treatment of advanced stage PTLD. Discontinuation of immunosuppression is recommended as first line intervention, while chemotherapy represents the most frequent therapeutic option for patients who fail the front-line treatment.[5,6] Both these strategies seem of limited value for patients developing aggressive lymphomas several years after a transplant.[3,4] Indeed, immunosuppression discontinuation is ineffective and life-threatening side effects secondary to chemotherapy are very frequent, resulting in a median survival ranging from 1 to 9 months only.[3,4]

Since the majority of PTLD derive from B-lineage lymphocytes, the administration of anti-B monoclonal antibodies represents a rational option to improve the patients' outcome, avoiding the risk of graft rejection due to immunosuppression discontinuation and minimizing the systemic toxicity secondary to chemotherapy. In fact, the administration of anti-B-cell murine monoclonal antibodies (anti-CD21 and anti-CD24) to a large cohort of patients was able to induce a sustained remission in about 64% of cases.[7] Nevertheless, it was shown that the

efficacy of this treatment was limited to early-onset PTLD, while the lymphoproliferative disorders occurring late after SOT were invariably resistant.[7] Recently, a new chimeric anti-CD20 monoclonal antibody (Rituximab, IDEC-C2B8, Roche, Basel, Switzerland) has been employed to treat non-immunocompromised patients with relapsing or refractory diffuse large cell non-Hodgkin's lymphoma (DLCL) and encouraging results have been reported in about 20% of the patients.[8] Compared to the murine antibodies this antibody has several advantages, including direct lysis of B-cells, reduced immunogenicity and a longer half-life.[9] Despite the low number of patients so far treated, rituximab administration has been reported to be safe and efficient for patients with PTLD occurring early after SOT or allo-BMT.[10-12] However, the safety and the efficacy of this antibody in patients developing aggressive PTLD several years after transplantation are still unknown. Here, we report our experience with rituximab administration in patients developing aggressive lymphoma more than two years after SOT.

Design and Methods

Patients

From March 1990 to February 2000, 29 patients were referred to our Hematology department because of the development of a lymphoproliferative disorder after a heart, kidney or liver transplant. Here, we report on 5 patients who developed aggressive lymphoma more than two years after SOT and who were treated with rituximab. In all patients the diagnosis of PTLD was obtained by morphologic examination of biopsy specimens. Patients were studied to detect the site of lymphoproliferative disease by computed tomographic (CT) scan of the chest and the abdomen and bone marrow biopsy. Table 1 summarizes the clinical characteristics of these patients.

Histology, immunophenotype and molecular evaluation

Biopsy specimens were fixed and stained for conventional histology examinations. Immunophenotypic studies were performed on paraffin-embedded tissue using the avidin-biotin complex technique with microwave antigen retrieval and a panel of anti-B and anti-T monoclonal antibodies, including the anti-CD20 monoclonal antibody.[13] Lymphoproliferative disorders were classified according to criteria proposed by Frizzera *et al.*,[14] and subsequently reclassified in accordance with the recommendations of the Society of Hematopathology.[15] Representative non-fixed portions of the specimens were used for high molecular weight DNA isolation as previously described.[16] Southern blotting analysis was performed according to a standard protocol.[16] Briefly, 15 μg of DNA were digested with restriction enzymes and the restriction fragments size-fractionated in 0.8% agarose gel and transferred to nylon membranes. Then, filters were hybridized with ^{32}P random oligonucleotide-labeled probes overnight at 65°C, washed under stringent conditions and exposed for autoradiography. Rearrangements of heavy chain immunoglobulin (IgH) genes were assessed using the enzymes BglII and HindIII/BamHI and an IgHJ6 probe spanning sequences of the JH gene region.[17] Rearrangements of c-myc oncogene were assessed using the EcoR1 or HindIII enzymes and a genomic probe for the second exon of human c-myc.[16] The presence of EBV genome in tissue samples was evaluated using the HindIII and BamHI enzymes and a 3.4 kb BamHI fragment of the EBV DNA (FF41 strain) (kindly provided by Dr. M. Minden, Ontario Cancer Institute, Toronto, Canada).[16] A positive control was included in all experiments. Moreover, false negative results for the presence of EBV genome were excluded by rehybridization of filters with house-keeping genes.

Table 1. Clinical profile of patients.

Patients	*Age at diagn./sex (years)*	*Organ transplant*	*Immunosuppressive treatment*	*Time from transplant to PTLD (months)*	*Clinical findings*	*Clinical stage*
1	3/M	Liver	FK506	29	Abdominal mass	II Bulky*
2	21/F	Heart	CsA	102	Lateral-cervical adenopathy	I Bulky
3	24/M	Heart	CsA + AZA	95	Retroperitoneal and meso-gastric adenopathy	II Bulky
4	12/F	Heart	CsA + AZA	80	Fever, lateral-cervical and retroperitoneal adenopathy, mediastinum enlargement, focal spleen lesions	IIISB
5	70/M	Heart	CsA + AZA	144	Lateral-cervical adenopathy	II

*FK506 = tacrolimus; CsA = cyclosporin A; AZA = azathioprine; *Bulky disease is defined as any lymph node or extranodal mass measuring 10 cm or more in its largest dimension.[22]*

Table 2. Morphology and molecular characteristics of PTLD.

Patient	*Histology*	*EBV genome*	*IgH configuration*	*c-Myc configuration*
1	DLCL*	N	R	R
2	DLCL	N	R	G
3	DLCL	N	R	G
4	DLCL	P	R	G
5	DLCL	N	R	G

**DLCL = CD20-positive diffuse large cell lymphoma; N = negative; P = positive; R = rearranged; G = germ line.*

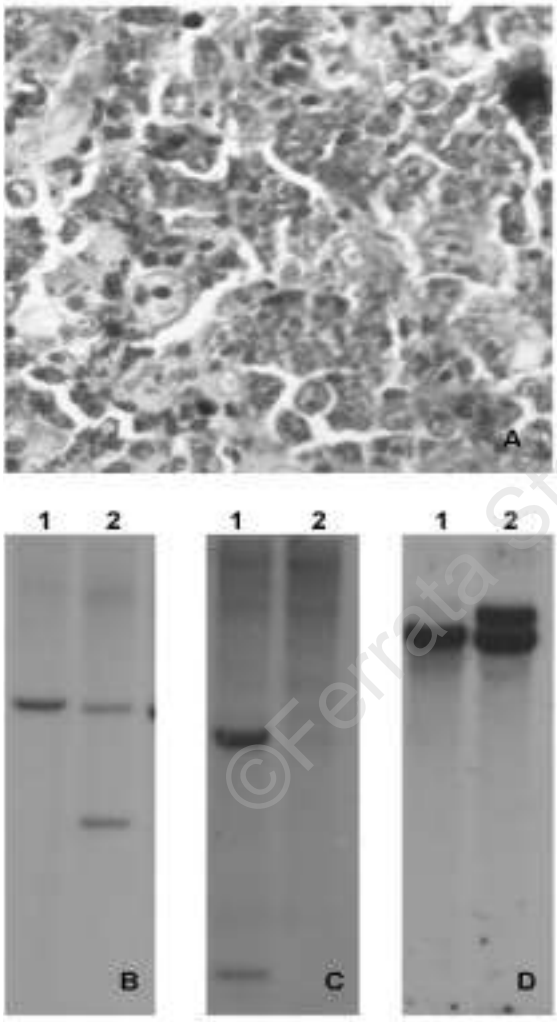

Figure 1. A representative case of late-occurring diffuse large cell non-Hodgkin's lymphoma after a liver transplant. Lymph node biopsy stained with hematoxylin and eosin shows large cells mixed with reactive lymphocytes (original magnification, ×250) (panel A). Southern blot analysis shows the rearrangement of IgH genes (panel B, line 2), the absence of EBV genome (panel C, line 2) and the rearrangement of c-myc oncogene (panel D, line 2). Lines 1 of panels B and D illustrate the germ line configuration for IgH and c-myc genes, respectively, while line 1 of panel C represents a positive control for EBV genome integration.

Treatment and response evaluation

In all patients with PTLD, as first-line treatment we reduced the immunosuppressive therapy by decreasing cyclosporin A (CsA) dose to maintain a trough level below 100 ng/mL and by discontinuing azathioprine (AZA) or tacrolimus (FK506).[3] For patients with localized and/or resectionable lesions, reduction of immunosuppression was associated with surgical excision. Chemotherapy and/or radiotherapy were initiated when lymph node or extranodal enlargement persisted or progressed 2-3 weeks after reduction of the immunosuppression.[3] From 1998, the evidence that immunosuppression discontinuation alone was ineffective for late-occurring lymphomas[3] prompted us to start chemotherapy and/or radiotherapy immediately in this group of patients. When the chimeric anti-CD20 monoclonal antibody (rituximab) became available, it was administered to patients with CD20-positive lymphoma developing severe side effects secondary to chemotherapy, or as consolidation treatment for patients undergoing radiotherapy. The antibody was provided by Roche for compassionate treatment and administered to patients after informed consent. All patients but one received weekly intravenous doses of rituximab (375 mg/m^2) for a total of four doses. One patient received a total of seven doses. Before rituximab infusion all patients received premedication with paracetamol and antihistamine drugs. The response to treatment was evaluated at the end of rituximab administration and complete remission was defined as complete regression of all clinical (physical and radiographic) disease evidence for at least four weeks. Partial remission was defined as a reduction by 50 percent or more in the size of lesions measurable in two dimensions. Absence of response or disease progression was defined as reduction in lesion size by less than 50 percent or increase in lesion size, respectively. Relapse was defined as reappearance of malignant lymphoma in a patient who had previously achieved a complete remission.[18]

Case reports

Case #1. A 3-year old boy, 29 months after receiving an orthotopic liver transplant, developed an abdominal mass. Clinical staging by CT scan demonstrated a bulky neo-formation involving the ileocecal tract (Table 1). FK506 was discontinued and the child was treated with surgical resection of the involved intestinal field. Histology and immunophenotype revealed a CD20 positive diffuse large cell lymphoma (DLCL) (Figure 1). Molecular analysis of the biopsy demonstrated monoclonal rearrangement of the IgH genes, rearrangement of the c-myc oncogene and absence of the EBV genome (Table 2 and Figure 1).

One month after surgery, we documented a local relapse of the disease and multiple liver biopsies demonstrated liver necrosis due to severe graft rejection. The child was treated with a single intravenous dose of cyclophosphamide (200 mg), but chemotherapy was immediately discontinued because of the rapid and progressive liver dysfunction. Rituximab was administered for three weeks, as compassionate treatment. The treatment was well tolerated and one week after the last dose of rituximab no evidence of lymphoma was detected by ultrasound scan of the abdomen. B-lymphocytes rapidly disappeared from the peripheral blood after the first antibody administration. Because of the irreversible liver deterioration due to graft rejection a second orthotopic liver transplant was performed followed by immunosuppression with FK506. Three weeks after transplantation four additional weekly cycles of rituximab were repeated in the attempt to reduce the risk of tumor recurrence. The post-operative period was not complicated by any episode of acute rejection or infection. With a follow-up period of 30 months, the child is doing well, without evidence of lymphoma and still receiving FK506 to prevent graft rejection of the second liver transplant. B-lymphocyte count recovered 6 months after the last dose of rituximab.

Case #2. A 21-year old woman, 102 months after heart transplantation, developed a rapidly growing mass in the neck. A total body CT scan showed a bulky neo-formation involving the lateral-cervical lymph nodes (Table 1). Histology and immunophenotype of the lymph node biopsy showed a CD20-positive DLCL. Molecular analysis demonstrated a monoclonal rearrangement of IgH genes and the lack of EBV genome (Table 2). Local radiotherapy (40 Gy) was started immediately and resulted in a rapid reduction of the neoplasm. Because of the high risk of relapse and the poor outcome of this subset of late-aggressive lymphoma,[3] consolidation treatment with four weekly doses of rituximab was given and well tolerated. As expected, B-lymphocytes rapidly disappeared from the peripheral blood after the first dose of rituximab and recovered 6 months later. With a follow-up of 20 months the patient is in complete remission and still receiving cyclosporin A which has never been withdrawn completely.

Case #3. A 24 year-old man, 95 months after heart transplantation developed a rapidly growing abdominal mass. CT scan showed extensive enlargement of retroperitoneal lymph nodes with a bulky neo-formation at the meso-gastric level (Table 1). Histology, immunophenotype and molecular analysis of a laparoscopic biopsy showed CD20 positive DLCL with a clonal IgH gene rearrangement and lack of EBV-DNA (Table 2). The massive abdominal tumor burden prompted us to consider the opportuneness of a weekly chemotherapy program (P-VABEC)[3] associated with discontinuation of AZA and reduction of CsA. Partial remission was obtained after the first three chemotherapy cycles, which were given with remarkable delay because of a prolonged pancytopenia after each cycle. Rituximab administration was started to avoid both the further delay in administration of an effective anti-lymphoma treatment and the severe chemotherapy-related myelosuppression. This treatment was well tolerated and induced complete disappearance of the retro-peritoneal lymph nodes and an additional reduction of the bulky meso-gastric lesion, as demonstrated by ultrasound abdomen analysis at the end of rituximab administration. Unfortunately, this clinical response was very short since one month later rapid tumor re-growth was observed and the patient succumbed after additional chemotherapy treatment.

Case #4. A 12-year old girl, 80 months after heart transplantation developed fever associated with lateral-cervical lymph node enlargement. Node biopsy demonstrated the occurrence of a DLCL positive for CD20 antigen expression. Molecular analysis revealed clonal IgH gene rearrangement and EBV-DNA integration (Table 1). In addition to lateral-cervical adenopathy, total body CT scan revealed enlargement of the mediastinum, involved retroperitoneal lymph nodes and a large focal lesion of the spleen (Table 1). As described for patient #3, concomitantly with AZA discontinuation and CsA reduction, we started the weekly P-VABEC chemotherapy protocol.[3] This treatment was interrupted after two cycles because of severe gastrointestinal bleeding requiring the patient's admission to the intensive care unit. Clinical re-staging showed a limited reduction of adenopathy after chemotherapy. In order to avoid rapid re-growth of the tumor in the absence of chemotherapy treatment, rituximab was administered immediately. The treatment was well tolerated and produced complete disappearance of adenopathy and partial regression of the focal spleen lesion. After one month, because of a rapid increase in serum lactate dehydrogenase (LDH) level, along with an otherwise unexplained fever, we performed gallium-67 scintigraphy that demonstrated multiple abdominal areas of tumor re-growth. An aggressive chemotherapy protocol was administered and the patient is still alive and on treatment.

Case #5. A 70-year old man, 144 months after heart transplantation, developed multiple lymph node enlargements in the neck (Table 1). Histology and immunophenotyping of a lymph node biopsy showed

CD20-positive DLCL. Molecular analysis demonstrated a monoclonal rearrangement of IgH genes and the lack of EBV genome (Table 2). The administration of AZA was stopped and local radiotherapy (40 Gy) was started immediately. As described for patient #2, consolidation treatment with four weekly doses of rituximab was given and well tolerated. With a follow-up of 12 months the patient is in complete remission and still receiving CsA which has never been withdrawn completely.

Discussion

We suggest that the humanized anti-CD20 monoclonal antibody rituximab can be safely administered to patients with aggressive CD20-positive DLCL occurring late after SOT. However, a positive clinical outcome can be expected only in patients in whom surgery or radiotherapy has achieved significant tumor regression.

The apparently beneficial impact of rituximab in patients with localized aggressive lymphoma is supported by the observation that these lymphomas, when occurring late after transplant, are rarely cured by local treatment alone.[3,4] The first patient we treated clearly documents the aggressive nature of these lymphomas since he presented with bulky DLCL showing c-myc oncogene rearrangement and rapid tumor re-growth after surgery. The plausible clinical benefit obtained by rituximab in this case is supported by the evidence of tumor regression and by the observation that this patient still remains in complete remission despite the continuous immunosuppressive treatment with FK506 necessary to prevent graft rejection of the second liver transplant. Rituximab was administered as consolidation treatment after local radiotherapy for patients #2 and 5. Even though we cannot demonstrate the anti-tumor activity of rituximab objectively in these two patients, the advantage of rituximab administration is suggested by the improved disease-free survival compared to our historical controls[3] and by the evidence that local radiotherapy alone is associated with a high relapse rate even in non-immunocompromised patients with bulky aggressive lymphoma.[19] The impairment of B-lymphocytes induced by four doses of rituximab is more prolonged than that reported after the administration of anti-B murine antibodies (usually two weeks)[7] and reflects the longer half-life of the chimeric antibody, secondary to its humanized structure. Nevertheless, none of our patients experienced severe infectious complications during or after treatment with rituximab, suggesting that this molecule does not further impair the immune competence of these patients.

The clinical effect obtained by rituximab in the two patients with advanced clinical stage (patients #3 and 4) was of limited significance. Several hypotheses can explain this result. First, it is likely that the achievement of a significant clinical benefit with monoclonal antibodies requires conditions of minimal tumor burden. This may be related to the inadequate local concentration of the molecule within bulky tumor lesions as well as to its rapid removal from the circulation when large tumor masses are present. Second, DLCL occurring late after SOT are biologically different from the polyclonal PTLD occurring early after SOT or allo-BMT which have been successfully treated with rituximab.[10-12] In this respect it is worth noting that normal B-lymphocytes are always and reproducibly lysed by the anti-CD20 monoclonal antibody i*n vitro* while the tumor killing of non-Hodgkin's lymphoma-derived CD20-positive cell lines can be highly heterogeneous.[20] The mechanisms of such heterogeneity may depend on the amount of CD20 molecules expressed on the cell surface and possibly on the role of complement inhibitor receptors such as CD55 and CD59.[20] It is tempting to speculate that EBV-driven early PTLD are sustained by the polyclonal unrestricted outgrowth of B-lymphocytes very similar to otherwise normal B-lymphocytes while late-occurring lymphomas may have a more heterogeneous expression of CD20 antigens as well as of complement inhibitor receptors. Moreover, the expression of EBV-related antigens by early PTLD is crucial for the generation of an EBV-specific immunocompetence and the initial tumor debulking induced by the antibody may favor the re-expansion of specific autologous cytotoxic T-lymphocytes, which can allow the clinical remission in these patients to be maintained. Contrariwise, the truly neoplastic transformation, characteristic of late lymphomas, and the frequent absence of EBV-associated antigens in these tumors may reduce the possibility of obtaining sustained immunologic control of the disease.

In conclusion, we suggest that reduction of tumor burden, suitable for consolidation with rituximab, remains the major goal for patients with diffuse aggressive lymphoma occurring late after SOT. Protocols combining rituximab and chemotherapy/radiotherapy should be evaluated in collaborative studies.[21] Moreover, systematic use of hematopoietic growth factors and complete discontinuation of immunosuppression during chemotherapy treatment may reduce their side effects[6] and maximize antitumor activity in this peculiar subset of patients.

Contributions and Acknowledgments

GP and AR designed the study and prepared the manuscript. GP carried out the molecular evaluations. TM carried out the histology examinations. RF, GT, PV, BG followed the patients included in the study. RF, BG and TB contributed to the discussion of the paper and approved the final version to be submitted.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Potential implications for clinical practice

Rituximab may improve the clinical outcome of patients developing localized aggressive lymphoma several years after solid organ transplant.

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