
SURVEILLANCE AND TREATMENT OF LIVER TRANSPLANT RECIPIENTS FOR CANDIDIASIS AND ASPERGILLOSIS

M.A. VIVIANI¹, A.M. TORTORANO*, C. MALASPINA*, M. COLLEDAN**,
G. PAONE**, G. ROSSI**, G. BORDONE*** and A. PAGANO*

*Istituto di Igiene e Medicina Preventiva - Università degli Studi di Milano
Ospedale Maggiore Policlinico - Via F. Sforza, 35 - 20122 Milano - Italy.

**Centro per il Trapianto di Fegato - Università degli Studi di Milano
Ospedale Maggiore Policlinico - Via F. Sforza, 35 - 20122 Milano - Italy.

***Istituto di Anestesiologia e Rianimazione - Università degli Studi di Milano
Ospedale Maggiore Policlinico - Via F. Sforza, 35 - 20122 Milano.

Key words: Opportunistic fungal infections - Liver transplant - Antifungal treatment

Between June 1988 and May 1991 88 orthotopic liver transplants and 1 liver and pancreas transplant were performed at the Liver Transplantation Department of the Ospedale Maggiore of Milan. All the patients underwent mycological surveillance and received antifungal prophylaxis with oral amphotericin B (6000 mg/day) or oral or intravenous fluconazole (200 mg/day) from the time of their transplant. The incidence of *Candida* colonization was 67%. Fluconazole was superior to oral amphotericin B in the treatment of *C. albicans* colonization (9/9 vs 6/15), but less effective in the treatment of colonization by other *Candida* spp. (0/3 vs 3/3). Deep-seated candidiasis developed in 5 patients, caused by *C. albicans* in 4 cases and *C. krusei* in 1. *C. albicans* infection resolved rapidly with fluconazole in 2 subjects, with intravenous amphotericin B alone in 1, and with amphotericin B plus flucytosine in the other. On the contrary, *C. krusei* infection did not respond to treatment with amphotericin B combined with flucytosine. Aspergillosis was diagnosed in 11 patients, of whom 4 died from invasive aspergillosis, despite 15 and 26 days of amphotericin B treatment in 2. In another patient invasive aspergillosis, diagnosed a few hours before retransplantation, improved with liposomal amphotericin B, but this man died from cytomegalovirus infection one month later. Aspergillosis was eradicated by itraconazole in 4 other patients and by topical amphotericin B in 2 whose infection was localized to surgical wound.

INTRODUCTION

The survival of liver transplant recipients has improved in recent years, but infections, mycoses included, are still an important cause of morbidity and mortality in the first 2 months following transplantation (1, 2, 4, 8). From the start of its activity in 1983, the Liver Transplantation Department of the Ospedale Maggiore Policlinico of Milan has used a mycological surveillance protocol. During the first 4 years of surveillance (3, 5) aspergillosis was diagnosed in 8 subjects, causing death

in 5. In addition, colonization by yeasts was detected in 23/36 (64%) patients at the time of transplantation or during the first month following surgery. Deep-seated candidiasis developed in 7 of the colonized patients, 2 of whom died. These observations led us to perform a randomized study comparing oral amphotericin B with oral or intravenous fluconazole to identify the most effective antifungal in the prevention and treatment of *Candida* colonization. The preliminary results have been recently reported (6).

The present paper reports the frequency of fungal infections observed in the last 3 years compared with the

¹ Corresponding author.

previous period (3, 5). It also describes our experience with the use of new drugs and formulations in the prevention and treatment of opportunistic mycoses.

PATIENTS AND METHODS

Between June 1988 and May 1991, at the Liver Transplantation Department of the Ospedale Maggiore Policlinico of Milan, 88 orthotopic liver transplants (OLT_X) were performed on 81 patients (OLT_X 47 to 61 and 63 to 134) and a liver and pancreas transplant in one patient (OLT_X 62). One of the 8 patients, who underwent retransplantation, received his first graft in 1986. Survival was over 24 hours in 81 patients. Fifteen of the transplant recipients were children (mean age 6.4 years, range 7 months - 14 years).

The indications for transplantation were hepatic cirrhosis in 38, cholestatic disease in 23, hepatic tumor in 12 and fulminant hepatic failure in 9.

All the patients underwent mycological surveillance as previously described (3, 7), starting immediately before transplantation and continuing during the postoperative period in the Intensive Care Unit. The protocol included cultures of biological samples from several body sites performed on alternate days and screening for anti-*Candida* antibodies.

The standard immunosuppressive regimen consisted of steroids and cyclosporin A. Rejection episodes were treated by increasing the steroid dose or with a cycle of monoclonal anti-human T cell antibodies.

All patients received antifungal prophylaxis from the time of their transplant for at least 4 weeks. The antifungal used for OLT_X 47 to OLT_X 60 was oral amphotericin B (6000 mg/day). The later patients (OLT_X 61 to OLT_X 134) were entered in a randomized study that compared oral amphotericin B (6000 mg/day) with oral or intravenous fluconazole (200 mg/day).

RESULTS AND DISCUSSION

Candida colonization was diagnosed in 46 of 81 patients at the time of their first liver transplant and in 3 of 8 at retransplantation. Six other subjects became colonized during postoperative course. The incidence of *Candida* colonization was 67%. The species most frequently involved was *Candida albicans* (43/55 cases, 78.2%). *C. krusei* was responsible in 4 cases, and *C. glabrata* and *C. tropicalis* in one case each. In 6 patients colonization was mixed: *C. albicans* and *C. glabrata* in 4, *C. albicans* and *C. krusei* in one, and *C. glabrata* and *C. krusei* in one.

In the randomized study performed on 51 patients to evaluate the efficacy of fluconazole compared with oral amphotericin B in the prevention

and treatment of *Candida* colonization, fluconazole was superior to oral amphotericin B in the prevention of colonization (12/12 vs 6/8) and in the treatment of *C. albicans* colonization (9/9 vs 6/15). But fluconazole was less effective in the treatment of other *Candida spp.* colonization (0/3 vs 3/3). Patients who did not respond to fluconazole were colonized by *C. glabrata* and/or *C. krusei*, species which are however known to be insensitive to this drug. These 3 patients responded to amphotericin B administered intravenously in 2 cases and orally in one.

Deep-seated *Candida spp.* infections developed in 5 (6.2%) of the 81 patients who survived for over 24 hours (Table 1). The species involved were *C. albicans* in 4 patients (OLT_X 62, 70, 101/104 and 118) and *C. krusei* in one (OLT_X 65/68). The yeasts were repeatedly isolated from mucous membranes in all patients; from abdominal drains in 3 patients and from bile in 2. In the patient (OLT_X 62), who received liver and pancreas transplant, *C. albicans* was isolated from the pancreas removed on day 3 and from 2 bile samples subsequently. The *C. albicans* infections resolved rapidly with fluconazole in 2 cases, with intravenous amphotericin B alone in one and with amphotericin B combined with flucytosine in one. The *C. krusei* infection did not respond to combined treatment with amphotericin B and flucytosine, and autopsy revealed an abdominal abscess caused by the yeast.

Aspergillosis was diagnosed in 11 patients (13.6%). It was caused by *Aspergillus fumigatus* in 10 and by *A. flavus* in one (Table 2). The *Aspergillus* species were repeatedly isolated from the respiratory secretions of 7 patients, one of whom (OLT_X 81) did not receive specific antifungal treatment since he died the day the mould was isolated. Two subjects (OLT_X 65/68 and 112) died of invasive aspergillosis after, respectively, 15 days of therapy with amphotericin B and flucytosine and 26 days of monotherapy with amphotericin B. Three other patients (OLT_X 49, 92 and 111), including a child with cystic fibrosis, were treated successfully with itraconazole (200-400 mg for 75-240 days). In one patient (OLT_X 64/66) invasive pulmonary aspergillosis was diagnosed a few hours before retransplantation and he was started on treatment with liposomal amphotericin B (AmBisome, Vestar Inc., USA) during the operation. Administration of this preparation was continued at a dose of 3 mg/Kg/day for 33 days until death occurred due to cytomegalovirus infection. Disseminated aspergillosis, diagnosed in a 3 year old girl (OLT_X 131), had an extremely rapid course and she died on day 23 following transplantation, after only 2 days of treatment with intravenous amphotericin B. In another patient (OLT_X 61) *A. fumigatus* was isolated in 7 bile samples obtained from a Kehr's drain. This patient was treated with itraconazole and the drain was removed. *A. fumigatus* was isolated from secretions of the surgical wound in 2 other patients (OLT_X 90 and 91) in whom cross-infection in the ward was suspected.

TABLE 1. - Course of deep-seated candidiasis.

OLTX	<i>Candida</i> species	Yeast isolated from	Day of 1st positive culture post transplant	Antifungal therapy	Outcome
62	<i>C. albicans</i>	removed pancreas, bile (2)	3	iv FLU for 18 days	infection cured; patient alive
65/68	<i>C. krusei</i>	abdominal drain (6)	51/2*	iv AMB + 5FC for 15 days	infection persisted; death
70	<i>C. albicans</i>	abdominal drain (10)	3	iv AMB + 5FC for 15 days	infection cured; death
101/104	<i>C. albicans</i>	bile (4)	47/6*	iv/oral FLU for 29 days	infection cured; patient alive
112	<i>C. albicans</i>	abdominal drain (15)	7	iv AMB for 26 days	infection cured; death

() = number of positive samples; * = day after 2nd transplant; FLU = fluconazole; AMB = amphotericin B; 5FC = flucytosine.

TABLE 2. - Course of aspergillosis.

OLTX	<i>Aspergillus</i> species	Fungus isolated from	Day of 1st positive culture post transplant	Antifungal therapy	Outcome
49	<i>A. fumigatus</i>	bronchial secretions (10)	42	ITR cps 400-200 mg for 120 days	infection cured; patient alive
61	<i>A. fumigatus</i>	bile (7)	52	ITR cps 300 mg for 18 days	infection cured; patient alive
64/66	<i>A. fumigatus</i>	bronchial secretions (15)	9	liposomal AMB for 33 days	infection improved; death from CMV
65/68	<i>A. fumigatus</i>	bronchial secretions (3)	55/6*	iv AMB + 5FC for 15 days	death from invasive aspergillosis
81	<i>A. flavus</i>	bronchial secretions (2)	10	—	death from invasive aspergillosis
90	<i>A. fumigatus</i>	surgical wound (2)	6	topical AMB	infection cured; death, no aspergillosis at autopsy
91	<i>A. fumigatus</i>	surgical wound (6)	10	topical AMB	infection cured; patient alive
92	<i>A. fumigatus</i>	bronchial secretions (9)	12	ITR cps 400 mg for 75 days	infection cured; patient alive
111°	<i>A. fumigatus</i>	bronchial secretions (6)	1	ITR oral solution/ cps for 240 days	infection cured; patient alive
112	<i>A. fumigatus</i>	bronchial secretions (7) nasal/oral secretions (5)	4	iv AMB for 26 days	death from invasive aspergillosis
131	<i>A. fumigatus</i>	abdominal drain (4)	19	iv AMB for 2 days	death from invasive aspergillosis

() = number of positive samples; * = day after 2nd transplant; ° = child with cystic fibrosis; ITR = itraconazole; cps = capsules; AMB = amphotericin B; 5FC = flucytosine.

Comparison with previously reported data on the first 46 transplants performed at our Center (3, 5) shows that whereas the frequency of deep-seated candidiasis was lower in the last 3 years (6.2% vs 19%) the incidence of *Candida* colonization was similar in the two periods (67% vs 64%). The incidence of *C. krusei* rose (10.9% vs 4.2%) whereas that of *C. albicans* and *C. glabrata* remained the same (78.2% vs 75% and 10.9% vs 12.5%). The frequency of aspergillosis decreased (13.6% vs 22%), as did the fatality rate (36.4% vs 62.5%, 4/11 vs 5/8 cases). This can be attributed to greater experience in both diagnosis and patient management and to the availability of new drugs and formulations. Itraconazole in capsules has proven to be effective in the treatment of aspergillosis, and the administration of oral solution dissolved in cyclodextrin has allowed treatment during the first days after transplantation. With liposomal amphotericin B high doses of the drug (3 mg/Kg/day) have been administered without toxic effects.

REFERENCES

1. Andrews W., Siegel J., Renard T. et al. (1991): Prevention and treatment of selected fungal and viral infections in pediatric liver transplant recipients - Clin. Transplant. 5: 204-207.
2. Kusne S., Dummer J.S., Singh N. et al. (1988): Infection after liver transplantation. An analysis of 101 consecutive cases - Medicine 67: 132-143.
3. Rossi G., Tortorano A.M., Viviani M.A. et al. (1989): *Aspergillus fumigatus* infections in liver transplant patients - Transplantation Proc. 21: 2268-2270.
4. Tollemar J., Ericzon B.G., Holmberg K. and Andersson J. (1990): The incidence and diagnosis of invasive fungal infections in liver transplant recipients - Transplantation Proc. 22: 242-244.
5. Tortorano A.M., Viviani M.A., De Matteo W. et al. (1988): Infezioni fungine nel trapiantato di fegato - Atti del 33° Congresso Nazionale della SIIMPSP - CIC Edizioni Internazionali, pp. 843-846.
6. Viviani M.A., Tortorano A.M., Malaspina C. et al. (1991): *Candida* colonization in orthotopic liver transplantation (OLT): fluconazole versus oral amphotericin B - International Symposium on Drugs and the Liver - Milano - July 3-5, 1991.
7. Viviani M.A., Tortorano A.M., Piazza T. et al. (1986): Candidosis surveillance in Intensive Care Unit patients - Bull. Soc. Fr. Mycol. Med. 15: 121-124.
8. Wajszczuk C.P., Dummer J.S., Ho M. et al. (1985): Fungal infections in liver transplant recipients - Transplantation 40: 347-353.