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PRESENT STATUS OF THE CLUSTER TRANSPLANTATION AND ITS VARIANTS

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INTRODUCTION

Upper abdominal exenteration with organ transplantation has been used to treat a selected group of patients with non-resectable upper abdominal malignancies (1). With the exenteration, most of the structures deriving from the embryonal foregut are removed, allowing potentially complete circumscription of certain hepatic, bile duct cell, duodenal, gastric and pancreatic malignancies which may have spread to the surrounding lymph nodes or adjacent organs.

PATIENTS AND METHODS

The organs excised are the liver, pancreas, spleen, stomach, duodenum, and variable portions of the proximal colon. The organs replaced are variable. Three different transplantation replacement techniques have been used: liver-pancreas-duodenum "en-block" (original cluster) (1), liver only (modified cluster) (2), and liver-pancreatic islets (3).

Original Cluster, (Group 1)

Twenty one patients were treated with the original cluster procedure between July 1988 and January 1990 (group 1). The indications are shown in Table 1. The patients were beyond help with conventional treatment, and in most of them resections, chemotherapy, irradiation, or combinations of these modalities already had been tried.

The first 15 patients of this group had

immunosuppression with cyclosporine, OKT3 induction with a 5 or 10 day course, and prednisone to which azathioprine was added if needed. In the other 6 patients the immunosuppression was with FK 506 and steroids (4,5).

Modified Cluster, (Group 2)

Eighteen patients had the same exenteration but with liver placement only between April 1989 and December 1989. All the patients except one were treated with the same cyclosporine cocktail used in the first 15 patients of Group 1. The exceptional patient was treated with FK 506 and steroids. The tumor diagnoses are shown in Table 2.

Liver-Islets (Group 3)

After abdominal exenteration, these 9 patients had liver replacement and pancreatic islet transplantation (3) under FK 506 and steroids between January 1990 and April 1990. OKT3 was given if necessary to control rejection. The tumor diagnoses (Table 3) were similar to those in Groups 1 and 2.

RESULTS

Group 1

After 11 to 29 months of follow-up, 8 of the 21 patients are alive (38%) and 6 of them (28.5%) are free of recurrence (Table 1). Seven of the 9 deaths resulted from technical complications and infections, usually at an early time. Tumor recurrence occurred later and was responsible for 6 deaths (Table 1). Two of these patients had metastases beyond the resection margins at the time of operation. The best survival was of patients with sarcomas and neuroendocrine tumors, and the poorest with duct cell carcinomas. Positive lymph nodes in the specimen was a poor prognostic finding.

TABLE 1

Primary Pathology	Alive	NED	AWD	DOD
7 Duct Cell CA	1	1	0	3
4 Carcinoid	3	2	1	0
3 Sarcoma	3	2	1	0
2 Cholangio CA	1	1	0	0
2 HCC	0	0	0	1
1 Adenoca Gallbladder	0	0	0	1
1 Adenoca Colon	0	0	0	1
1 Neuroendocrine	0	0	0	0

TABLE 1 --- Survival by diagnosis in the original cluster patients (Group 1). NED = no evidence of disease, AWD = alive with disease, DOD = dead of disease.

Group 2

With a follow-up ranging between 12 and 20 months, 6 patients are alive (33%) and 4 of them (22%) are free of recurrence. The causes of death, time of death, and prognostic influence of tumor diagnosis were no different than in Group 1 (Table 2). As in Group 1, some patients (2 examples) had metastatic tumors beyond the resection margins at the time of operation but this was not appreciated until later.

TABLE 2

Primary Pathology	Alive	NED	AWD	DOD
9 Cholangio CA	4	3	1	2
6 HCC	0	0	0	5
1 Carcinoid	1	1	0	0
1 Leiomyosarcoma	1	0	1	0
1 Neuroendocrine	0	0	0	1

TABLE 2 --- Survival by diagnosis in the modified cluster patients (Group 2). For legend, see Table 1.

Group 3

Six of the 9 patients are alive after 8 to 11 months of follow-up. One patient died of recurrent cancer after 178 days, and 2 others died earlier from infection; all three were insulin dependent at the time of death. Of the 6

patients who are alive, 4 are without evidence of tumor recurrence and all 6 are insulin free. Table 3 shows the survival by tumor diagnosis.

TABLE 3

Primary Pathology	Alive	NED	AWD	DOD
2 Cholangio CA	2	2	0	0
2 Adenoca Pancreas	1	1	0	0
2 HCC	1	1	0	1
1 Sarcoma	1	0	1	0
1 Adenoca Colon	1	0	1	0
1 Neuroendocrine	0	0	0	0

TABLE 3 --- Survival by diagnosis in the liver and pancreatic islet patients (Group 3). For legend, see Table 1.

DISCUSSION

These operations had a high mortality from technical complications which always led to infections. In Group 1 recipients, the pancreas component of the graft was responsible for 4 fatal complications: pancreatitis and pancreatic abscess (2), and pancreatitis and rupture of an arterial pseudoaneurysm (2). Severe weight loss was observed in patients of all 3 groups and those in Groups 2 and 3 required prolonged parenteral hyperalimentation (in some to the present time). Group 2 patients had the further handicap of being diabetic. Control of this complication in Group 3 patients by islet transplantation was noteworthy.

The use of FK 506 seemed to make the control of rejection easier, but the case material was too limited and complex to allow comparisons with cyclosporine cocktail regimens. Patients treated with FK 506 (6 in Group 1, one in Group 2, and 9 in Group 3) had very low steroid requirements compared to those treated with conventional immunosuppression. Acute rejection usually could be reversed with a bolus of methylprednisolone and increased doses of FK 506. In an FK patient of Group 1, graft versus host disease (GVHD) was unequivocally diagnosed with sex kharyotyping

performed by in situ hybridization of the Y chromosome; the donor was a male and the recipient female. She was treated successfully with increased steroid therapy.

The type and the extent of tumor were the chief non-technical factors influencing later survival. Patients who had macroscopic or microscopic lymph-node involvement had a very high rate of recurrence. However, our experience suggests that a selected group of patients could benefit from this radical surgical approach. Afterwards, adjuvant chemotherapy or irradiation should be considered.

The nutritional problems suffered by patients in all 3 groups (especially Groups 2 and 3) suggest that future trials may require the addition of a gastric component to the replacement graft. This would have to be placed in mainstream continuity with the alimentary tract. Such new options may become feasible with the better immunosuppression made possible with FK 506 (4,5).

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