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Fetal Stem Cells Use in Complex Treatment of Cancer of the Head of Pancreas

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Abstract

Objective: to identify efficacy of fetal stem cells use in treatment of the patients with cancer of *caput pancreatis;* to summarize all hematology advantages and positive effects on overall condition of the patients, improvement of their life quality.

Material and methods: we studied 15 patients who had been suffering from cancer of the head of pancreas and were administered treatment by use of fetal stem cell (FSCs) suspensions at Cell Therapy Center EmCell. All such patients underwent general and clinical examination over 1 and 3 months after FSCs transplantation: we were using functional CT and ultrasonography (US) for assessment of organs of abdominal cavity.

Results: FSCs treatment contributed to better life quality in patients of the MG who revealed improvement of asthenia syndrome components: reduced fatigability, less exhaustion and emotional instability; decrease in hyperesthesia and phenomena of vegetative dysfunction. In the patients of the MG leucocytes count was significantly reduced in comparison with indexes which were recorded prior to FSCs treatment. Such results might be an evidence of reduction in inflammation of biliary ducts, as well as decreased paracancerous inflammation in the patients under study.

Conclusion: Combined use of FSCs and conventional therapy for the patients with *caput pancreatis* cancer is well-tolerated by all patients, leads to reduced intoxication contributing to improved tolerability of standard anti-cancer therapy and promotes better life quality in the cancer patients. Positive changes in cell-mediated immunity were recorded in the patients after treatment.

Keywords

Caput pancreatis cancer; Fetal stem cells; Mechanical jaundice; Percutaneous transhepatic cholangiography

Introduction

All statistic evidences have it recorded that over the recent 100 years oncology pathology shifted from the tenth to the second place due to the levels of morbidity and death of patients worldwide; oncology illness yields the first place only to cardiovascular diseases. Each year 10 million of individuals develop cancer. In accordance with data of the WHO, mortality rate among the cancer patients will increase by 45% until 2030, if compared with the same rate in 2007 [1,2]. As representatives of the WHO reported, the number of mortality cases caused by cancer will continue gradual growth among the European population [3]. In this respect, as they claim, over 40% of cancer diseases would be prevented if people maintained a healthy way of life and also mechanisms of cancer timely detection were improved. In countries of Europe mostly people with low and middle income are susceptible to cancer diseases who can realize such risk factors in less extent and those having a limited access to effective health care [2,3].

Pancreatic cancer (PC) - is one of the most important medical problems worldwide. Mortality rate resulting from PC is holding the 5th place all over the world, whereas in the USA – such a mortality rate occupies the 4th place [4].

PC ranks the second place in respect to causes of death among malignant processes in males. PC occurs more frequently in elderly people and it is a great health concern throughout developed countries with their large number of elderly aged men. In the developed countries patients with PC constitute around 15% of all tumor diseases among males compared to 4% of men suffering from PC in the countries which are still being developed [3].

PC is hardly susceptible to treatment and this could be connected with both peculiarities of pancreatic gland functioning and with late diagnosis of this problem among the population. Most of pancreatic tumors are revealed at the advanced stages when malignancy can severely strangulate adjacent organs and had already resulted in metastases [5]. Even though pathology process is localized in the *caput pancreatis* only 5% of such patients could be amenable to surgery, over 95% of such patients can receive just palliative therapy. Operative excision of PC is possible when tumor had been diagnosed at the early stage, remained within the pancreas and did not metastasize to surrounding organs [6]. One can resort to organ saving surgery intervention in the young patients who are capable to go through a likely operative intrusion. During surgery treatment, part of the gland or the whole pancreas is removed; sometimes together with the part of stomach and duodenum, common bile duct and lymphatic nodes lymphatic nodes involved into the tumor process tumor process [7]. After operation such patients demand a life-long use of medicines along with herbal enzymes and insulin. When tumor excision is not possible owing to its deep invasion, doctors usually resort resort to performing range of manipulations to enable bile excretion and improve patient's general state. For instance, endoscopic retrograde cholangiopancreatography (ERCP) belongs to likely manipulations. During operation on the patient with PC, the catheter is installed in order to relieve bile outflow through the narrowed part. Every 3-4 months the catheter demands replacement with a new one. Percutaneous transhepatic cholangiography (PTCG) is one more intervention to improve general condition of the patients with PC. PTCG suggests placement of the stent into the region with narrowing of the bile duct. Radiology therapy is prescribed immediately after operative intervention to prevent development of the new foci of tumor cells which could remain in the patient's organism. It can also relieve pain in the patients with advanced cancer. Chemotherapy for PC is ineffective; it can result in complications itself and it is commonly used in a complex with radiotherapy for unresectable tumors helping to improve the general condition of such patients [8,9]. Hormonal

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therapy of cancer is revealed to be enough effective because there are a lot of receptors of estrogen on tumor cells of pancreas which stimulate their growth. Nevertheless, even in neglected cases an extending of effective palliative care can significantly increase life quality at different stages of the disease [10].

It has been uncovered that both development of neoplasms and the methods of radiotherapy along with chemotherapy can induce a marked depressive effect on immune and hematopoietic systems of the human organism. Affection of immunity as well as myotoxicity effects induced by cytostatic drugs in majority of cases tend to restrict performance of contemporary chemotherapy and radiology treatment. FSCs obtained from human fetal liver can be an effective method for prophylaxis and treatment in the above cases of complications. Therefore, FSCs suspensions could be used not only as the method of adaptive immune therapy, but also contribute to prevention of complications affecting blood formation process in the patients and and allow maintaining chemotherapy within a scheduled regimen.

In view of this, a search for alternative methods of therapy is of actual importance. Clinical studies with allogenic transplantation of stem cells in patients with PC have been conducted which had an objective of studying two-year survival of the patients suffering from PC [11], and such studies are still being in progress. In use of stem cells one can maintain high effectiveness of treatment for the patients with PC which is stipulated by paracancerous inflammation and mechanical pressure to the biliary ducts. In particular, inflammation and toxicity effects on biliary ducts are reduced owing to a decrease of total and direct bilirubin in blood. Growth of tumor itself can be inhibited – possibly because of mechanism of T-cells mediated response of graft-versus-tumor (GVT) - the likely effect as in solid tumors [12-14], whereas psychological state of the patient is improved.

Objective of the study was determining a dynamics of biliary pigments in the patients suffering from *caput pancreatis* cancer treated by use of FSCs in complex therapy.

Material and Methods

Within a period from 2003 to 2016 we treated 15 patients suffering from *caput pancreatis* cancer in Cell Therapy Center EmCell among which 10 patients had stage III cancer process (T3N1M0), in 4 persons - stage II cancer was confirmed (T2N0M0), and 1 patient revealed stage IV cancer (T4N1M0). All patients were distributed in the following way: 10 individuals were included into the main group (MG) who were performed treatment by use of FSCs of fetal liver, brain and progenitor cells of connective tissue in complex with conventional medical therapy. The control group (CG) allocated 5 patients who were solely treated according to the standard protocols. Average age of the patients in the MG made up 60.9 ± 9.13 years, whereas age ranges in the CG patients were 65.4 ± 7.6 years. All patients in both groups were males. Diagnosis of PC was established based on the clinical results, patient's history data, findings of ultrasound and the results of computed tomography (CT) with bolus contrast enhancement (abdominal cavity organs) along with endoscopic retrograde cholangiopancreatography values which allow detecting foci of tumor infiltration ("filling defects") the same as laboratory findings contributed to diagnosis-making among the patients. Diagnosis of cancer has been histologically verified in the patients of both groups. At baseline and following treatment by FSCs the SF 36 scale for life quality evaluation was used to control life quality among the patients.

All patients underwent standard medical therapy by use of gemcitabine 1000 mg/m^2 intravenously for the 1st, 8th and 15th day of treatment.

Fetal stem cells transplantation was performed immediately after the 1st course of chemotherapy.

For treatment we used cryopreserved suspensions with inclusion of pluripotent stem cells (PSCs) extracted from 7-12 weeks gestation human cadaveric fetuses, received as a result of legal abortions owing to social indications, or for the reason of family planning. All women signed the informed consent document for medical use of proper abortive material. Collection of material was performed in accordance with ethical-moral and legislative principles of work with biological tissues. All donors of the aborted material were practically healthy women; they revealed negative test findings to blood infections. This study was approved by the local ethical committee which holds a sitting in Kyiv City Emergency Clinical Hospital located on the address: Kyiv City, 3 Bratislavska Street.

The whole biotechnology process of suspension preparing consisted in stem cells extraction from the fetal liver; assessment of stem cells viability as well as cells programmed cryopreservation, bacteriology and virology studies. Immediately before FSCs administration the cryopreserved suspensions were defrosted using a water-bath thawing at temperature of 37°C along with simultaneous assessment of stem cells viability.

Cryopreservation was made under protection of 5% dimethyl sulfoxide (DMSO) according to 3 stage program of freezing with starting velocity of 1°C/min. and initiation of crystals formation. Stem cells viability was also directly identified prior to transplantation along with trepan blue application as a staining method. Calculation was performed in parallel using Goryaev chamber and 1450001 TC10 TM Automated Cell Counter.

Prior to cryopreservation viability of stem cells in the suspension constituted 85.0 ± 3.0%. After storage in a low temperature cryobank (t -196°C) and following suspension heating on a water bath at the temperature +37.5 ± 0.12°C stem cells viability rate was not less than 71.0 ± 1.01%.

The patients were administered fetal liver stem cells using i.v. drip-feed infusions as soon as cells had been washed off using DMSO. Volume of a therapeutic dose per each administration was individually selected and it constituted not less than 0.3 mL of cell suspension with inclusion of not less than 0.30 × 10^8/mL nucleated cells and CD34+ progenitor cells ranging from 0.50 to 2.53 × 10^6/mL per each infusion. Amount of viable stem cells in the suspensions made up 71.0 ± 10.0%.

In order to define the phenotype of cells a method of immunophenotyping was used: cells are stained by the specific andtibody to CD, associated with fluoroscent 4',6-diamidino-2-phenylindole (DAPI) dye followed by analysis using flow cytometer (FCM). This study was conducted by means of system for flow cytometry of FACSCalibur (workspot with installed Multi Test software connected to the FCM) Becton Dickinson (USA), with additional use of BD Multitest™ IMK Kit.

All patients signed their informed consent prior to beginning of FSCs treatment. General clinical examination was performed before treatment, over 1 and 3 months following FSCs therapy.

We used 3 types of FSCs suspensions which were defrosted after cryopreservation in order to be administered; specifically, intravenous infusion of stem cell suspensions obtained from fetal liver 7-12 weeks of gestation in amount not less than 1.3 ± 0.68 mL. The number of nucleated cells was not less than 12.4 ± 2.1 × 10^6 in 1 mL per one infusion. Stem cells of fetal brain were injected subcutaneously in the volume of 2.1 ± 0.3 mL with cells count not less than 2.81 × 10^6 in 1 mL per infusion, whereas suspension with progenitor cells of connective tissue was administered subcutaneously in a volume of 0.8 ± 0.2 mL with a number of cells not less than 1.63 × 10^6 in 1 mL per infusion.

Prior to transplantation of FSCs, over 1 and 3 months after therapy, an overall effectiveness of treatment was evaluated according to the patient's state of health, his objective status and the laboratory findings: common blood count, blood biochemistry values (ranges of bilirubin, ALT, AST, blood amylase etc.) as well as evaluation of life quality of the patients by means of the scale SF 36.

Significance of the mean values was assessed by use of Student's t-criteria (for parametric statistics) and with application of Mann - Whitney U test (for non-parametric statistics). Difference was regarded as statistically significant if $p<0.5$. Statistical processing of data was performed with the help of software Statistika v.8.0.

Results

All patients during the first day after FSCs administration revealed a syndrome of early post-transplantation improvements: they reported a fit of energy, much power; their sleep became deeper and appetite increased. No single case of complications or adverse reactions was reported among the patients after transplantation of FSCs. In addition, no evidence of graft-versus-host disease (GVHD) was remarkable.

Over 1 month based on general hematology indexes the following results had been recorded: values of hemoglobin and erythrocytes neither in the MG nor in the CG patients were deteriorated. Leucocytes count was significantly reduced in the patients of the MG (10.65 ± 2.65 × 10^6/L) over 1 month after therapy in comparison with indexes (15.25 ± 4.83 × 10^6/L) recorded prior to treatment ($p<0.05$); such a trend also remained over 3 months after FSCs transplantation - 11.2 ± 2.65 × 10^6/L, $p<0.05$. (Table 1) This could be an evidence of decreased inflammation in biliary ducts, as well as paracancerous inflammation was reduced.

In study of the values of cell-mediated immunity after chemotherapy we recorded inhibition of some immunity components (Table 2).

Inhibition of immunity was recorded both in the MG and CG before treatment which was identified as reduced both absolute lymphocytes count and their subpopulations: CD3+, CD4+, CD8+ lymphocytes; the same as CD4+/CD8+ ratio.

Following FSCs transplantation patients in the MG recorded elevation of absolute lymphocytes count over 1 month after treatment. Indexes of CD3+ lymphocytes increased to (1.06 ± 0.40) × 10^9/L compared to baseline (0.26 ± 0.01) × 10^9/L and absolute count of CD4+ was elevated to (0.55 ± 0.17) × 10^9/L compared to baseline (0.15 ± 0.01) × 10^9/L, $p<0.05$; whereas ratio between CD4+/ CD8 + was also somewhat elevated (1.50 ± 0.02) versus (1.14 ± 0.21) prior to treatment. Patients in the CG did not reveal a feasible improvement in these components of immunity, even though likely tendency was also observed among the patients.

Such changes in cell-mediated immunity were not stable. Thus, over 3 months after FSCs treatment, patients of the MG revealed the range of CD8+ which approached the same level in healthy patients; whereas the level of CD4+ was decreased to the values baseline. In the patients of the CG we only observed a tendency to stabilization of such parameters.

In biochemistry blood results significant reduction of total bilirubin was identified among patients of the MG (22.07 ± 2.94)

Table 1: Dynamics of CBC results before and after FSCs treatment in patients of the MG and CG.

	MG			CG		
Values	**Before treatment**	**Over 1 month**	**Over 3 months**	**Before treatment**	**Over 1 month**	**Over 3 months**
Erythrocytes (RBC) g/L	4.125 ± 0.45	4.234 ± 0.34	4.257 ± 0.46	3.97 ± 0.007	4.054 ± 0.212	3.954 ± 0.014
Hemoglobin (Hb) g/L	126.1 ± 19.94	132.7 ± 11.98	112.5 ± 19.95	130 ± 12.72	129.8 ± 7.77	122 ± 13.43
Platelets (PLT) g/L	260.5 ± 61.52	243 ± 60.96	223.5 ± 50.21	213 ± 13.43	215.2 ± 19.79	207.8 ± 32.52
Leucocytes (WBC) g/L	15.25 ± 4.83	10.65 ± 2.65*	11.2 ± 2.65*	5.9 ± 4.38	5.8 ± 5.16	6.44 ± 5.30
Erythrocytes sedimentation rate (ESR) mm/h.	42.5 ± 15.35	38.5 ± 11.55	39.5 ± 13.6	23 ± 1.41	30 ± 0	36.2 ± 1.41*

Note: * - p<0.0: Significance between the indexes of the MG and CG before and after treatment (over 1 month; over 3 months).
** - p<0.001: Significance between the indexes of the MG and CG before and after treatment (over 3 months).

Table 2: Dynamics of biochemistry test results before and after FSCs treatment in patients of the MG and CG.

Values	MG			CG		
	Before treatment	**Over 1 month**	**Over 3 months**	**Before treatment**	**Over 1 month**	**Over 3 months**
Total bilirubin mcmol/L	32.52 ± 7.10	22.07 ± 2.94*	24.06 ± 4.19*	32.57 ± 3.33	37.59 ± 0.42	41.34 ± 1.27
Direct bilirubin mcmol/L	22.76 ± 6.85	12.54 ± 3.78*	14.92 ± 3.92*	24.31 ± 5.73	28.26 ± 3.46	30.74 ± 0.56*
Indirect bilirubin mcmol/L	8.69 ± 4.70	9.53 ± 2.45	8.35 ± 3.89	8.26 ± 2.40	9.51 ± 3.04	10.60 ± 1.83
ALT, U/L	252.5 ± 32.31	205 ± 23.81	242 ± 22.41	208.4 ± 3.53	217 ± 6.36	225.8 ± 7.07
AST, U/L	185.5 ± 42.21	159.5 ± 30.92	184 ± 30.84	128.4 ± 65.76	134.6 ± 53.74	135.4 ± 48.08
AST/ALT ratio	0.714 ± 0.09	0.765 ± 0.13	0.75 ± 0.11	0.92 ± 0.28	0.598 ± 0.212	0.582 ± 0.17
Gamma-glutamyltransferase, (GGT) U/L	24 ± 11.06	22.5 ± 5.27	23 ± 3.95	33.2 ± 9.19	39 ± 6.36	43 ± 5.65
Blood glucose mmol/L	5.26 ± 0.52	4.99 ± 0.52	4.8 ± 0.49	5.37 ± 0.21	5.21 ± 0.14	5.33 ± 0.28
Amylase U/L	50 ± 13.95	62 ± 19.54	66 ± 23.74	74.4 ± 9.19	68.2 ± 12.02	59.6 ± 15.5

Note: * - p<0.05: Significance between the indexes of the MG and CG before and after treatment (over 1 month; over 3 months).
** - p<0.001: Significance between the indexes of the MG and CG before and after treatment (over 1 month; over 3 months).

mmol/L over 1 month if compared to (32.52 ± 7.10) mmol/L before FSCs therapy (p<0.001). Over 3 months after treatment this score revealed (24.06 ± 4.19) mmol/L in comparison with baseline (32.52 ± 7.10) mmol/L (p<0.001). Significant decrease of direct bilirubin was also remarkable (22.765 ± 6.85) mmol/L before treatment compared to (12.545 ± 3.78) mmol/L over 1 month after FSCs therapy (p<0.001); and (22.765 ± 6.85) mmol/L versus (14.92 ± 3.92) mmol/L (p<0.001) over 3 months after therapy among the patients of the MG. Whereas the patients in the CG revealed a tendency to increase in the ranges of total and direct bilirubin: over 1 month after treatment total bilirubin elevated as high as to (37.59 ± 0.42) mmol/L versus (32.57 ± 3.33) mmol/L baseline (p<0.05), over 3 months it was (41.34 ± 1.27) mmol/L versus (32.57 ± 3.33) mmol/L prior to treatment (p<0.05). Direct bilirubin ranges were higher by (28.26 ± 3.46) mmol/L over 1 month after treatment in comparison with the parameters recorded baseline – (4.31 ± 5.73) mmol/L, (p<0.05), over 3 months the same value made up (30.74 ± 0.56) mmol/L compared to baseline (24.31 ± 5.73) mmol/L, (p<0.05).

As a result, owing to reduction in total and direct bilirubin, a slight decrease of intoxication can be maintained resulting in less itching of the skin in the patients.

In out-patient department we performed ultrasound and CT investigation of abdominal cavity organs - the above studies recorded no signs of disease progression among the patients in the MG.

We also observed improvement of asthenia syndrome components in patients of the MG: reduced fatigue, less exhaustion and emotional instability; decrease in phenomena of hyperesthesia and vegetative dysfunction.

Following FSCs transplantation life quality improvement was also recorded in accordance with assessment by SF36 scale for the patients of the MG: mental component baseline made up 46.0, whereas over 1 month after treatment it was 47.6, and over 3 months the same value composed - 47.0; physical health component constituted 31.6, over 1 month - 33.0; and over 3 months following FSCs treatment this score made up 32.5 (Figure 1).

In the patients of the CG general condition was gradually deteriorated: their baseline mental component made up 44.0, over 1 month after treatment it reduced to 42.6, over 3 months the same value made up only - 41.0; whereas physical component of health constituted 30.5 before treatment, over 1 month it was - 30.0, and this value reduced to 28.1 over 3 months in the CG (Figure 2).

Temporary improvement after FSCs therapy had a favorable effect on a general health in patients of the MG; treatment did not increase

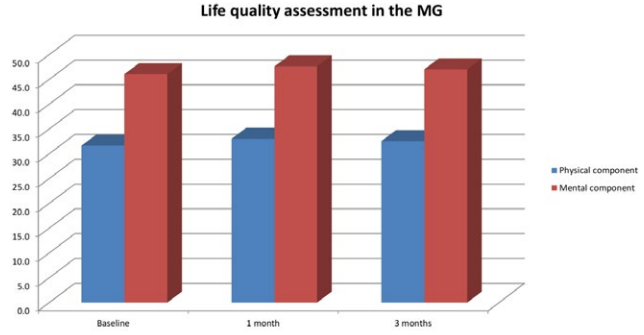

Figure 1: Life quality assessment among the patients of the MG.

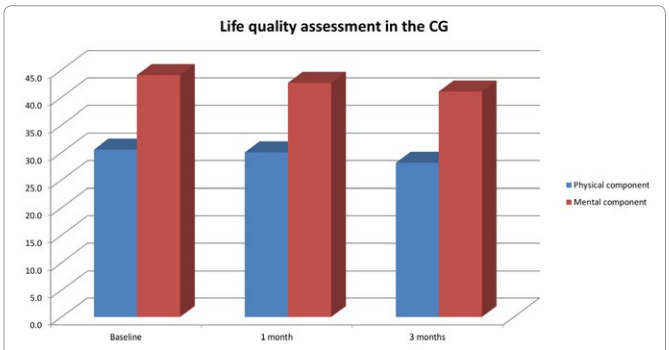

Figure 2: Life quality assessment among the patients of the CG.

the median of survival rate among the patients, but reduced suffering of the patient.

Discussion

Mechanism of action of FSCs is not fully investigated and further large-scale studies are being conducted. Probably increase of anti-tumor immunity after allogenic transplantations for the cases with hematology malformations is akin to such a possibility (with the help of; owing to this) and donated T-cell mediated immunity with graft-versus-tumor (GvT) effect could be proven effective for solid tumors. Increased life quality among the patients could be possible due to lowering of depression and this promotes such a mode of treatment using stem cells showing its explicit reliance, however, further scientific studies are still demanded in this direction.

Conclusions

FSCs suspensions which were used in complex treatment of pancreatic cancer contribute to:

• Improvement of hematology indexes, specifically reduction of leucocytes in the patients of the MG;

• Positive changes in cell-mediated immunity were presented as elevated level of CD3+ and CD4+ lymphocytes as well as CD3+ / CD4+ ratio over 1 month following FSCs therapy;

• Decrease in the ranges of total and direct bilirubin among the patients of the MG;

• Improvement of general state among the patients resulting in improved life quality.

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All authors emphasize absence of financial and other conflict interests in respect of the submitted manuscript. The content of the manuscript is original and it has not been published or accepted for publication, either in whole or in part, in any form. No part of the manuscript is currently under consideration for publication elsewhere.

All works with fetal material were conducted in accordance with current Ukrainian legal and ethical standards. This study was approved by the local ethics committee established on the base of Kyiv City Clinical Emergency Hospital located on the address: 3 Bratyslavska str., Kyiv City, Ukraine.

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