

FUJIKURA H, URAKAMI A, IWAMOTO S, YAMASHITA K,
YOSHIDA K, KIMOTO M, SUGIU K, TAKEDA M and TSUNODA T:
Seven Cases of Primary Carcinoma of the Duodenum 137-142

Primary carcinoma of the duodenum is rare compared with gastric or colorectal cancer and it is also a type of cancer for which it is difficult to make a preoperative diagnosis because it has no specific symptoms. In the last eight years, we treated seven cases (male 6, female 1) of primary carcinoma of the duodenum. Their mean age was 61 years old. As for the initial symptoms, three cases had epigastric pain, one case had jaundice and three cases were asymptomatic. Endoscopy and hypotonic duodenography were useful for the preoperative diagnosis in these cases. The tumors were located in the suprapapillary region in two cases, and in the infrapapillary region in five cases. All patients underwent surgery. Four cases underwent a pancreatoduodenectomy, two cases underwent local excision and one patient was unresectable. Histological examination revealed that six cases were well-differentiated adenocarcinomas, and one was a mucinous adenocarcinoma. Five of the seven patients had early stage duodenal cancer, resulting in a good prognosis. It is difficult to make an early diagnosis because carcinoma of the duodenum has no specific symptoms. Endoscopic screening of the second or third portion of the duodenum by gastroduodenoscopy would be useful to find early stage duodenal cancer. A precise preoperative diagnosis which determines the depth of cancer invasion is necessary for the choice of treatment.

【Objective】

In cases of attempted suicide, it has been noted that many subjects who making more serious attempts to commit suicide also tend to have mental disorders in the strict sense (ex. psychoses, depressive disorders or psychoactive substance use disorders) as compared with persons making less serious attempts. A clinical study review of cases of attempted suicide was performed to examine the relationship between the lethality of the means used in a suicide attempt and the seriousness of the physical consequences.

【Subjects】

Relevant information on 56 patients who were hospitalized in the Department of Psychiatry of Kawasaki Medical School Hospital, after attempting suicide and in whose treatment the author was directly involveds and 18 patients who attempted suicide and were hospitalized in other department of the same hospital for more than one week with whom the author had indirect involvement was examined.

【Methods】

All 74 patients were investigated retrospectively. For risk determination, patients were initially classified into a “high risk group” and a “low risk group”. However after it was found that some patients fit into neither category an “indefinable group” was established. In terms of the seriousness of the physical injuries sustained in the suicide attempts, patients were classified into a “severe injury group” and a “mild injury group”.

【Results】

There were 42 cases in the “high risk group”, 18 cases in the “low risk group”, and 14 cases in the “indefinable group”. There were 38 cases in the “severe injury group” and 36 cases in the “mild injury group”.

On the basis of the respective diagnoses, 85.7% of the patients in the “high risk group” were judged to suffer from mental disorders whereas the proportion in the “low risk group” was 55.6% and that in the “indefinable group” was 85.7%. In terms of the relationship between mental disorders and the extent of injuries, 84.2% of the patients in the “severe injury group” had mental disorders with the figure being 72.2% for the “mild injury group”. A comparison of the ratio of mental disorders to risk revealed a stainistically significant difference between the “high resk group” and the “low risk group” ($P=0.011<0.05$) by the chi-square test, but there was no statistically significant difference between the “high risk group” and the “indefinable group” ($P=0.685$). No statistically significant difference was found between the “severe injury group” and the “mild injury group” ($P=0.21$).

【Conclusion】

There is evidence that mental disorders more significantly correlate with the lethality of the means in attempted suicides than with the seriousness of the physical injuries, and that for attempted suicides it is very important to determine both the lethality of the means as well as the seriousness of the injuries. When attempting to determine risk, an “indefinable group” was found to exist, but the characteristics of this “indefinable group” more closely resembled those of the “high risk group” than the “low risk group”.

Objectives : To determine which staining evaluation method is best for determining the immunohistochemical expression of heat shock protein 27 (HSP 27), which could be the most significant prognostic factor in epithelial ovarian cancer patients.

Methods : Expression of HSP 27 was studied in 71 epithelial ovarian cancer patients by immunohistochemical staining. The relationship between survival analysis and the expression was determined by some staining evaluation methods ; Geisler's, Arts' and ours.

Results : Survival analysis using our 25% cut-off scale ($p < 0.01$) and one of Geisler's modified staining evaluation methods ($p < 0.05$) demonstrated that HSP 27 expression is significantly related to a poor survival rate, but this relationship did not reach statistical significance when evaluated by Arts' method, another method of Geisler's and our 50% cut-off scale. The mean HSP 27 staining score in deceased patients (6.16) was not significantly different from that in surviving patients (4.97) by Geisler's original staining evaluation method.

Conclusion : The current study data suggest that our staining evaluation method (25% cut-off scale) is the most satisfactory and that HSP 27 expression is significantly related to a poor survival rate.

Recently, there has been great expectation regarding the use of cell therapies such as hepatocyte transplantation and bioartificial livers to treat patients with liver failure. Improvement of differentiated cellular functions is of fundamental importance in hepatocyte-based biological therapies. The molecule of p21, known as WAF1, is a potent cyclin-dependent kinase inhibitor which regulates the transition from the G1 phase to the S phase in a cell cycle. Investigators have demonstrated that p21 transduction induces cellular differentiation in various cell lines. We used SV40Tag-immortalized human NKNT-3 hepatocytes in this study. A replication-deficient adenovirus vector, Ad5CMVp21, expressing a p21 gene under the control of the CMV promoter, was used to achieve efficient p21 delivery. A pTAT-p21 fusion protein was also utilized for transduction in NKNT-3 cells. Morphological alteration, cell-cycle progression, and protein expression of albumin, CYP3A4, and CYP2C9 were analyzed in the p21-transduced NKNT-3 cells. Immunofluorescent staining and Western blotting analysis for p21 showed efficient p21 transduction in the NKNT-3 cells using Ad5CMVp21 or pTAT-p21. Under cell cycle analysis, transduction of p21 caused G1-arrest in NKNT-3 cells, leading to differentiated hepatic phenotypes including a decreased N-C (nucleo-cytoplasmic) ratio, decreased cell density, and enhanced protein expression of albumin, CYP3A4, and CYP2C9. In the results presented here, we show that exogenous expression of p21 augmented cellular differentiation in immortalized human NKNT-3 cells.

Using a highly metastatic human testicular seminoma cell line, JKT-HM, a CDDP-resistant cell line, JKT/DDP, was established by long-term intermittent administration of a low dose of cis-diamminedichloroplatinum (II) (CDDP). CDDP-resistance was investigated in vitro by comparison of the growth curves, CDDP-sensitivity, and intracellular CDDP concentrations of the established cell line, JKT/DDP, the original human seminoma cell line, JKT-1, and its highly metastatic derivative, JKT-HM. The growth curve and doubling time of JKT/DDP were not significantly different from those of JKT-1 or JKT-HM in culture without CDDP. However, in the presence of CDDP in culture, there was a significant difference in the growth curve. Morphological observations revealed segmentation of the cytoplasm and aggregation of chromatin in JKT-1 and JKT-HM. In contrast, in JKT/DDP, spindle-shaped cells showed cobblestone growth. In addition, the IC_{50} values of CDDP determined by the collagen gel drop embedded drug sensitivity test (CD-DST) showed JKT/DDP to be significantly more resistant to CDDP than the other two cell lines. Therefore, a CDDP-resistant cell line was established. Next, we investigated the expression of the genes (Multidrug resistance 1, MDR 1; Multidrug resistance associated protein, MRP; Lung resistance-related protein, LRP; Glutathione-S-transferase π , GST- π) related to anticancer drug-resistance associated with the intracellular CDDP concentration and cytoplasmic CDDP metabolism in JKT-1, JKT-HM, and JKT/DDP. The intracellular CDDP concentration was lower in JKT/DDP than in the other two cell lines. mRNA expression of MDR 1, MRP, LRP, and GST- π was investigated by a real-time PCR. The expression levels of MDR 1, MRP, and GST- π were significantly higher in JKT/DDP than in JKT-1 and JKT-HM. It was suggested that JKT/DDP acquired CDDP-resistance, and that an increased active exudation of cytoplasmic CDDP was involved in the acquisition of this CDDP-resistance.

To examine the antifibrosis effect of interferon γ (IFN γ) and Rapa an immortalized human hepatic stellate cell line, TWNT-4, was established by introducing human telomerase reverse transcriptase (hTERT) into LI 90 cells. The TWNT-4 cells were confirmed to express platelet-derived growth factor β receptor (PDGF- β R) and α -smooth muscle actin (α -SMA) by immunostaining. Interferon γ (IFN γ), which is known to inhibit human hepatic stellate cell activation, could not inhibit collagen type 1 (α 1) under a condition of 24 hour incubation at more than 1000 U/ml concentration. Incubation of IFN γ at a low concentration of 100 U/ml, for 14 days, however, inhibit collagen type 1 (α 1) production in both RNA and protein levels. An immunosuppressive agent Rapa, also inhibited collagen type 1 (α 1) production proportionally at a concentration of 1 to 10 ng/ml. When both IFN γ and Rapa were added to the incubation medium for 14 days at the one tenth of the usual concentration of each drug, collagen type 1 (α 1) expression was equally inhibited. IFN γ and Rapa also inhibited production of TGF- β 1 hepatic stellate cell PDGF- β R, and α -SMA. Apoptosis of TWNT-4 cells occurred as a result of adenovirus-mediated TRAIL cDNA transfer. These results confirmed that IFN γ and Rapa inhibit collagen expression in hepatic stellate cells, resulting in an antifibrosis effect. Therefore these drugs could have a clinical application for the prevention of fibrosis in liver cirrhosis.

As a source for liver-targeted regeneration medicine, a supply of normal human hepatocytes is essential. However there are limitations to the supply of human liver from surgical resection. Therefore, the efficient use of a limited liver supply is required.

For this purpose it is extremely important to establish efficient techniques for the cell isolation and cold-preservation of isolated liver cells. As for the isolation of hepatocytes from surgically removed pig livers, dispase perfusion followed by collagenase digestion should yield hepatocytes with more than 90% viability.

Cold-preservation for eight hours using isolated pig hepatocytes in the following preservation media was compared ;

- 1) University of Wisconsin (UW) solution with ascorbic acid 2 glucoside (AA2G)
- 2) University of Wisconsin (UW) solution
- 3) 100% fetal bovine serum
- 4) Dulbecco's Modified Eagle's Medium supplemented with 10% fetal bovine serum

With the UW solution, viability, plating efficiency and ammonium clearance were well preserved after eight hours of cold-preservation.

UW+AA2G solution yielded the best preservation effect.

The use of AA2G inhibited activation of caspase-3, resulting in well-preserved cellular ATP levels.

Based on the above results, the UW+AA2G solution appeared to be most suitable for cold-preservation of pig hepatocytes. Clinical application for the cold-preservation of human hepatocytes can be expected.