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Pancreatic cancer remains one of the diseases with poor prognosis, and the most patients have no chance to be operated when they are diagnosed as pancreatic cancer. Their 5-year survival rate is less than 5%. Gemcitabine is one of the most effective chemotherapeutic drugs for pancreatic cancer, but the therapeutic effect is insufficient because many types of pancreatic cancer are resistant. We have reported that HSP27 was one of the important factors related to gemcitabine-resistance. We treated gemcitabine-resistant pancreatic cancer cells with interferon-gamma or KNK-437, which were reported as HSP27-suppressors, and showed the suppressive effects of HSP27 and combinatorial effects on inhibition of proliferation against gemcitabine-resistant pancreatic cancer cells.

AHCC is an extract of basidiomycete mushroom and includes polysaccharide, and has been used as health food to enhance the therapeutic effects and reduce the adverse effects of chemotherapy. In the present study we investigated the effects of AHCC on the expression of HSP27, and the effects of combinatorial treatment of AHCC and gemcitabine on the gemcitabine-resistant pancreatic cancer cells, and AHCC down-regulated HSP27 and showed an anti-proliferative effect on gemcitabine-resistant cells.
## Prognosis of pancreatic cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
<th>5 year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>128</td>
<td>58.6%</td>
</tr>
<tr>
<td>Stage II</td>
<td>192</td>
<td>51.0%</td>
</tr>
<tr>
<td>Stage III</td>
<td>1039</td>
<td>25.9%</td>
</tr>
<tr>
<td>Stage IVa</td>
<td>1809</td>
<td>11.9%</td>
</tr>
<tr>
<td>Stage IVb</td>
<td>4661</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

### Therapy and prognosis

<table>
<thead>
<tr>
<th>Method of therapy</th>
<th>5 year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td>12.2%</td>
</tr>
<tr>
<td>Palliative operation</td>
<td>0%</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>2.0%</td>
</tr>
<tr>
<td>Non-operation</td>
<td>0%</td>
</tr>
</tbody>
</table>

*SUIZOU* 2003 (Japanese).
Gemcitabine (gemzar, GEM), a drug used for chemotherapy against pancreatic cancer.

Figure from Pancreatic cancer: highlights from the 42nd annual meeting of the American Society of Clinical Oncology, Saif MW, JOP. J Pancreas (Online) 2006; 7:337-348.
## Materials 1: Pancreatic cancer cell lines

<table>
<thead>
<tr>
<th>cell line</th>
<th>differentiated</th>
<th>origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MiaPaCa-2</td>
<td>undifferentiated</td>
<td>pancreas</td>
</tr>
<tr>
<td>Panc-1</td>
<td>undifferentiated</td>
<td>pancreas</td>
</tr>
<tr>
<td>BxPC-3</td>
<td>poorly diff.</td>
<td>pancreas</td>
</tr>
<tr>
<td>AsPC-1</td>
<td>moderately diff.</td>
<td>ascites</td>
</tr>
<tr>
<td>PK45p</td>
<td>unknown</td>
<td>pancreas</td>
</tr>
<tr>
<td>PK59</td>
<td>unknown</td>
<td>pancreas</td>
</tr>
</tbody>
</table>

The cytotoxicity of gemcitabine (GEM) to the cells was evaluated by MTT assay

<table>
<thead>
<tr>
<th>cell line</th>
<th>MiaPaCa-2</th>
<th>Panc-1</th>
<th>BxPC-3</th>
<th>AsPC-1</th>
<th>PK45p</th>
<th>PK59</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50µg/ml</td>
<td>6.81</td>
<td>8.07</td>
<td>6.67</td>
<td>1.05</td>
<td>417.45</td>
<td>294.72</td>
</tr>
</tbody>
</table>

**GEM-sensitive lines**

**GEM-resistant**

2-DE pattern of MiaPaCa-2 (sensitive) and PK59 (resistant)

MiaPaCa-2 (GEM-sensitive)

PK-59 (GEM-resistant)

Five spots were expressed weakly in GEM-resistant cells than in sensitive cells.

Five spots were higher levels in GEM-resistant cells than in sensitive cells.
Expression analysis of HSP27 (2DE)

Sensitive lines

MiaPaCa-2  Panc-1  BxPC-3  AsPC-1

Resistant lines

PK45p  PK59


* p<0.05  ** p<0.01
Immunoblot analysis of HSP27

Materials 2: Acquired resistant cell line to gemcitabine

KLM1 (Sensitive line)

GEM 10µg/ml

1 w incubation

GEM free medium

2 w incubation

Repeat 4 times

KLM1-R (Resistant line)

MTT assay of KLM1 and KLM1-R

Int J Oncol. 2007 Dec;31(6):1345-50
Expression of HSP 27 in KLM1 and KLM1-R

KLM1

KLM1-R

HSP27

actin

Int J Oncol. 2007 Dec;31(6):1345-50
Decreasing resistance to GEM in HSP27-knocked down KLM1-R cells

![Graph showing growth inhibition](image-url)

Int J Oncol. 2007 Dec;31(6):1345-50
The immunopositive rate of HSP27 in progressive disease (PD) and stable disease (SD)
Survival Curves of Pancreatic Cancer Patients (HSP27-positive and HSP27-negative) treated with GEM (Kaplan-Meier)

Logrank test
P=0.0106

Int J Oncol. 2007 Dec;31(6):1345-50
Active hexose-correlated compound (AHCC), an extract of basidiomycete mushroom called Lentinula edodes, is composed of polysaccharides, amino acids, lipids and minerals. The predominant components of AHCC are oligosaccharides and their major portions are 5 kDa molecules named α1,4-glucans. AHCC is used as a health food to support the therapeutic effects and alleviate adverse effect of chemotherapy owing to immunomodulatory and antitumor effects of AHCC.
Expression levels of HSP family proteins in KLM1-R cells treated with AHCC.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Molecular Weight</th>
<th>AHCC (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSP27</td>
<td>27 kDa</td>
<td></td>
</tr>
<tr>
<td>HSP60</td>
<td>60 kDa</td>
<td></td>
</tr>
<tr>
<td>HSP70</td>
<td>70 kDa</td>
<td></td>
</tr>
<tr>
<td>HSC70</td>
<td>70 kDa</td>
<td></td>
</tr>
<tr>
<td>GRP78</td>
<td>78 kDa</td>
<td></td>
</tr>
<tr>
<td>Actin</td>
<td>43 kDa</td>
<td></td>
</tr>
</tbody>
</table>

Anticancer Res. 2014 Jan;34(1):141-6
The intensity of the HSP27/actin bands in KLM1-R cells treated with AHCC.

Anticancer Res. 2014 Jan;34(1):141-6
Cytotoxic effect of AHCC on KLM1-R cells.

Anticancer Res. 2014 Jan;34(1):141-6
The cytotoxic effect of the combinatorial treatment of AHCC and GEM on KLM1-R cells.

Anticancer Res. 2014 Jan;34(1):141-6
Expression levels of SOX2 in KLM1-R cells

Anticancer Res. 2014 (in press)
Expression levels of SOX2 in KLM1-R cells-2

\[ p < 0.001 \]

Anticancer Res. 2014 (in press) calculated by Student’s t test
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