Adenoviral p53 gene transfer and gemcitabine in three patients with liver metastases due to advanced pancreatic carcinoma

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Abstract

Background. Current therapies for adenocarcinoma of the pancreas do not improve the life expectancy of patients. Methods. In a non-randomized pilot trial we tested whether a local therapy based upon an adenoviral gene transfer of wild type p53 in combination with gemcitabine administration would be safe in patients with liver metastases due to pancreatic carcinoma. We report on the clinical course of three patients with respect to safety, tolerability and tumor response. Results. Transient grade III toxicities occurred with fever, leucopenia, elevation of AP, ALT, AST, GGT, while grade IV toxicity occurred for bilirubin only. Laboratory tests suggested disseminated intravascular coagulation in all three patients, but fine needle biopsies of liver did not show any histological evidence of thrombus or clot formation. Progression of liver metastases was documented in one and stable disease in another patient two months after treatment. However, a major improvement with regression of the indexed lesion by 80% occurred in a third patient after a single administration of $7.5 \times 10^{11}$ viral particles, and time to progression was extended to six months. Conclusion. The combination therapy of viral gene transfer and chemotherapy temporarily controls and diminishes tumor burden. Improvement of the toxicity profile is necessary. Further trials are warranted to improve treatment and life expectancy of patients suffering from fatal diseases such as pancreatic carcinoma.

Key Words: Adenovirus, p53 gene transfer, liver metastases, pancreatic carcinoma

Introduction

The prognosis of pancreatic carcinoma is poor. Most patients already have advanced disease at the time of diagnosis. The 5-year survival rate is around 10% and depends on the stage, with a median survival of only 6 months [1,2]. Surgery in the form of pancreaticoduodenectomy offers the only possibility of a cure [3]. However, the 5-year-survival rates after surgery do not exceed 20% in pancreatic carcinoma [2], due to early hepatic metastases. Specific mutations in a number of genes like K-ras, CDKN2A, BRCA2, SMAD4/DPC4 and p53 have been recognized as signature lesions involved in and causing progression of the disease. Among the mutated genes, the p53 tumor suppressor gene is altered in more than 70% of patients [4,5], which deprives cells of protection against ill-defined breakage-fusion-bridge cycles, and allowing for subsequent oncogenic alterations.

Gene transfer therapy could improve the treatment of pancreatic carcinoma, with adenoviruses being among the most promising vectors for this therapy [6]. The transfer of the wild-type tumor suppressor gene p53 into cancer cells in order to restore its lost function in DNA damage control was demonstrated to induce apoptosis in various cells in vitro and in the mouse model [7], which has prompted its introduction in antitumor strategies against pancreatic carcinoma. Indeed, increased tumor cell apoptosis and reduced cell growth in human pancreatic carcinoma cell line derived tumors has been demonstrated in nude mice after adenoviral p53 transfer [8,9]. Likewise, an adenoviral vector expressing p21, a downstream effector of p53, reduced tumor cell growth, presumably through reverting cell cycle from S to G0/ G1 phase [10]. Vector-mediated introduction of the wild-type retinoblastoma gene resulted in growth
inhibition but not apoptosis [11]. Several other strategies of gene transfer therapies for pancreatic carcinoma have been investigated in mice, among them suicide gene prodrug systems utilizing cytidine deaminase, thymidine kinase or UPRT [12–17], attempts to develop CaSM-antisense strategies [18], somatostatin receptor transfer [19] or ribozymes that modulate expression of K-ras [20].

However, a number of limitations dampened early hopes and have prevented the broader use of gene transfer therapies. Major among these are the risk of disseminating viral vectors, and the potential for severe toxicity sometimes seen with adenoviral vectors [21]. High doses systemic administration of non-replicating E1-deleted adenoviral vectors has caused hepatic necrosis and death in number of animal models including primates. Especially with increasing amounts of vector such as might be necessary to achieve an effective systemic dosage there is evidence for such toxicity [22,23]. Liver toxicity occurring after vector administration is substantially milder in replication incompetent than in replication competent vectors in animal modeling [24]. However, tolerability and the level of toxicity observed in phase I and phase II trials utilizing conditionally replication competent adenovectors to treat hepatocellular carcinoma or liver metastases of colorectal cancer have warranted further trials [25,26]. Still, hepatotoxicity is a major concern in treating tumors metastatic to the liver.

To date, there is still limited information available on clinical trials utilizing adenoviral gene transfer for metastatic pancreatic carcinoma, and few of the strategies explored in animal modelling have been evaluated for safety and efficacy in the treatment of human diseases. We conducted a phase I/II pilot study to treat patients with liver metastasis due to advanced pancreatic carcinoma with immunohistologically proven p53 mutation. An intravenous gemcitabine chemotherapy was followed on subsequent days by administration of a p53-expressing, replication incompetent adenoviral vector rAV/p53 via the coeliac artery.

### Materials and methods

#### Study design and patients

A non-randomized, non-controlled, open-label, phase I/II pilot study of a recombinant replication-defective and p53-expressing adenoviral vector in combination with weekly administration of gemcitabine (2',2’-difluorodeoxycytidine) has been initialized in patients with advanced stage of pancreatic carcinoma.

Patients between the ages of 18 and 75 years with histologically confirmed and metastatic carcinoma and stable or progressive disease which was considered to be incurable have been eligible. Those who had an identified measurable index lesion, immunohistochemical accumulation of p53 as evidence of its gene mutation, adequate performance status and laboratory tests and fulfilling all inclusion criteria were enrolled in the study.

The treatments were conducted as approved by the ethical board committee of the Dresden University of Technology. Informed consent was obtained from all patients prior to treatment. The patients received full supportive care.

#### Treatment schedule and vector

**Gemcitabine Therapy.** The treatment schedule is summarized in Table 1. Gemcitabine (Gemzar, Lilly Deutschland GmbH, Bad Homburg, Germany) at 1000 mg/m² was diluted in 100 mL normal saline and administered intravenously over 30 min once per week (on day 1, day 8, day 15 etc). In patient 2 and 3, gemcitabine has not been administered on day 8.

**Adenoviral Vector and Administration.** rAd/p53 (SCH 58500, Essex Pharma GmbH, München, Germany) is a serotype 5 based replication–defective adenoviral vector. An expression cassette containing the human cytomegalovirus immediate early promoter and enhancer element, the adenovirus serotype 2 tripartite leader and the human p53 wild type cDNA has been introduced into region E1 [29]. rAd/p53 was grown and purified according to standard procedures and in accordance with GLP/GCP. The IV treatment

### Table 1. Treatment Schedule.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>8</th>
<th>15</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>29</th>
<th>36</th>
<th>43</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rAd/p53, 2.5 × 10¹² v.p. Gemcitabine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>rAd/p53, 2.5 × 10¹² v.p. Gemcitabine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>rAd/p53, 7.5 × 10¹² v.p. Gemcitabine</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After a single day of Gemcitabine intravenously, rAd/p53 was injected into the celiac artery on the following day(s), followed by 1 d of intravenous Gemcitabine per week for three weeks.
formulation was kindly provided by Schering-Plough (SCH 58500, Essex Pharma GmbH, Munich, Germany).

Dosages of $2.5 \times 10^{12}$ viral particles twice on successive days (patients 1 and 2) and in a planned dose escalation $7.5 \times 10^{12}$ (patient 3) were injected into the coeliac artery in normal saline on days 2 and 3 in all patients and also on days 23 and 24 in patient 1 only. Administration was carried out with radiological control via a Terumo sidewinder catheter (5 F, length 100 cm, inner diameter 0.38 cm). Perfusion was visualized by injection of 30 mL UltravistTM.

Endpoints, assessment of efficacy and toxicity

Primary Endpoints, Toxicity. Patients were observed to detect any toxic effects related to any of the categories within the Common Toxicity Criteria (CTC Version 2.0) such as allergic, haematologic or cardiovascular complications, coagulopathy, constitutional, gastrointestinal, hepatic, infective, metabolic, neurologic, pulmonary, renal symptoms, pain and tumor lysis syndrome. Safety was assessed by review of laboratory studies. All laboratory studies were carried out according to commercial standard tests and the manufacturer’s instructions.

Histology. Ultrasound-guided fine-needle aspiration of the liver was done before and on day 4 after vector administration. Aspirates were snap-frozen in liquid nitrogen and stored at $-80^\circ$C. Sections of 8 μm were fixed in 3% paraformaldehyde in 1× phosphate-buffered saline (10× PBS: 1.3 M NaCl, 70 mM Na₂HPO₄, 30 mM NaH₂PO₄) prior to staining with hematoxylin-eosin.

Cryostat sections were immunostained for p53 (DO-1 anti-p53 monoclonal mouse antibody, Dianova, Hamburg, Germany). The specimens were exposed to the specific antiserum for 12 h at 4°C at dilutions of 1:100. The reaction was visualized using the avidin-biotin staining method according to the catalyzed signal amplification (CSA) system (Dako, Hamburg, FRG) with AEC chromogen (Immunotech, Hamburg, FRG). Slides were counterstained with hematoxylin, rinsed in water and mounted in glycerol gelatin (Sigma, Munich, FRG). As a control, the specific antiserum was replaced by an isotype-immune serum (Mouse IgG1, κ [anti-TNP], Pharmingen, Hamburg, FRG).

Secondary Endpoint, Assessment of efficacy. The response of the index lesion to the treatment was assessed by thin-layer computed tomography and positron emission tomography. Positron emission tomography was performed following a fasting period of at least 12 h. Scans were obtained over 60 min after IV injection of approximately 310 MBq $^{18}$F-Fluorodeoxyglucose. CT examinations were carried out every month following vector administration with month 2 examination being evaluated. Positron emission tomography was added at 2 months in case of regression or stable disease.

Results

Patient characteristics

Three male patients at 50 years (patient 1), 64 (patient 2), and 58 (patient 3) years of age were included in the study.

Painless jaundice and weight loss of 10 kg became apparent in patient 1 two months before enrolment at the age of 50 years. Ultrasound examinations revealed a tumor of the head of the pancreas and several lesions within the liver suggestive of metastases. Histological examination of an ultrasound guided fine needle aspiration of a liver lesion revealed a poorly differentiated adenocarcinoma of the pancreas. Jaundice was treated with biliary prosthesis. The patient had been enrolled after informed consent was obtained.

The pathological grading and staging was pTx Nx M1 G3, UICC stage IV. Positive immunoreactivity against p53 was seen in 90% of cells with 30% poorly, 40% intermediate and 30% strongly positive cells, corresponding to a Remmele score of 8 and a Confidential immunoreactivity score (IRS) of 3+.

Patient 2 complained of a lack of appetite, mild abdominal pain and loss of weight of 8 kg within 4 months prior to diagnosis at 64 years of age. Helicobacter pylori associated gastritis was treated without relief of his symptoms. A subsequent computed tomography of the abdomen showed a tumor of the body of the pancreas and metastases in the liver. Fine needle aspiration of a liver metastasis documented an adenocarcinoma of the pancreas. The patient had been enrolled after informed consent was obtained.

The tumor was staged and graded histologically as pTx Nx M1 G3, UICC stage IV. Positive immunoreactivity against p53 was seen in 100% of tumor cells. Exact immunoreactivity scores could not be determined.

In patient 3 at the age of 58 years cholecystectomy was performed 9 months before inclusion in the trial. Three months later the symptoms of dyspepsia, diarrhoea and meteorism recurrent and were accompanied by weight loss of 7 kg. Four months later he was diagnosed with a tumor in the head of the pancreas and underwent a partial duodenopancreatectomy (Whipple’s procedure). Pathology examination revealed a mildly differentiated tubulo-papillous adenocarcinoma of the pancreas. Five months later metastases in the liver were found. The patient was enrolled after informed consent was obtained.

The pathological grading and staging was pT2 N0 M0 G2 RO, UICC stage I, at the time of surgery. Positive p53 immunoreactivity was seen in 40% of cells with 50% poorly, 40% intermediate and 10%...
strongly positive cells among these, thus resembling a Remmele score of 2 and Confidential IRS of 2+.

After inclusion of three patients the study was halted because of safety concerns arising after a fatality that occurred in a human subject participating in a clinical trial for ornithine transcarbamylase deficiency [27,28] and observed grade III and grade IV toxicities in our own trail, and no further patients were treated in this protocol.

Assessment of toxicity

General performance and constitutional symptoms of patients. All patients had a Karnofsky index of 80% or higher, the BMI ranged between 22.3 and 23.8 (patient 1, 73 kg bodyweight at 181 cm height; patient 2, bodyweight 69 kg and 172 cm body height; patient 3 bodyweight 67.7 kg and 175 cm body height). Patients 1 & 2 developed chills and an increase of body temperature not exceeding 38.5°C. No immediate rise in body temperature was seen in patient 3, however, on day 8 he experienced convulsive abdominal pain accompanied by shivers and a temperature increase to 40.5°C 8 d after vector administration. The symptoms have been suggested to be related to bacterial cholangitis due to insufficiency of bile stent and resolved after change of the stent and administration of ciprofloxacin.

Cardiovascular. For all patients blood pressure and heart rate remained within the normal range after vector administration and on the following days. In patients 1 and 3 a slight decrease in blood pressure not falling below systolic 105 mmHg and diastolic 80 mmHg was observed upon immediate administration. The heart rate remained within the normal range, and no cardiovascular support was needed.

Hepatic toxicity. All patients showed an elevation of serum AST between 2.1 and 5.5 times (maximum 5.51 μmol/L*s) and of serum ALT between 1.38 and 2.8 times (maximum 3.85 μmol/L*s) compared to values before treatment (Figure 1). Total bilirubin levels ranged between 13.6 and 24 μmol/L, with a tendency to increase during progression of the disease and without notable impact of the administered therapy. A 2.5 fold increase (14.37 μmol/L*s) in lactate dehydrogenase was seen only in patient 3, who received the highest dose. Total protein and serum albumin decreased during the first 4 d, with minimal values when ALT and AST elevation reached maximum values. However, the total protein and serum albumin did not fall below the normal range. There have been no clinical signs of hepatic encephalopathy.

Coagulation profile. All patients showed a slight decrease of thromboplastin time. In two patients partial thromboplastin time increased up to 1.9 times above the upper limit of normal. Disseminated intravascular coagulation was present in all three patients as defined by elevation of D-dimers. D-dimers increased above the upper limit of normal (below 1,0 μg/mL) up to 4 fold in patient 1 (4.0 μg/mL), 1.9 fold in patient 2 (1.9 μg/mL) und 8 fold in patient 3 (8.0 μg/mL).

Blood. In all patients a decline in blood components was observed. Only in patient 3, who received highest dosage leukocytes fall to 1.9 × 10⁹ /L and platelets to 66 × 10⁹ /L.

Tumor lysis syndrome and related. Tumor lysis syndrome was absent in the patients. No apparent changes in kidney parameters were observed. The data is summarized in Table 2.

Histological findings. On day 4 after vector administration, fine needle aspiration of liver metastases was performed. The specimens demonstrated a mild to moderate fatty degeneration of hepatocytes with anisoneucleosis, slight cholestasis as well as chronic inflammation of the portal fields and within the lobuli. Of note, smaller arteries and portal vessels and sinusoids were devoid of histological signs of epithelial damage or thrombus formation. Besides this, necrotic cell clusters within the initial carcinomatous tissue were present (Figure 2).

Assessment of efficacy

Efficacy of treatment was evaluated using thin layer computed tomography and positron emission tomography scan examinations.

Patient 1. Computed tomography showed stable disease 2 months after vector administration. Positron emission tomography suggested decreased metabolic activity of the metastases. Radiologic and clinical progression were confirmed 3 months after vector administration.

Patient 2. Progression of liver metastases had to be confirmed after 2 months by computed tomography examinations. No further therapy was given.

Patient 3. Regression of liver metastases was confirmed in computed tomography 2 months after vector administration. The size of the index lesion decreased by 38% (from 31 mm × 24 mm to 22 mm × 21 mm). Likewise, a major improvement was demonstrated by positron emission tomography. The therapy was continued only with gemcitabine due to the closure of the trial; after 4 months computed tomography documented further regression of the index lesion.
to \(-80\%\) of initial size (13 \times 12 \text{ mm}), but 6 months later the patient experienced progression of disease. Data are depicted in Figure 3.

**Discussion**

We conducted a phase I/II pilot trial of adenoviral transfer of wild type p53 into hepatic metastases of pancreatic carcinoma in combination with weekly gemcitabine administration. Coeliac arterial infusion of the p53-expressing replication-incompetent adenovirus derivative was well tolerated at doses resulting in therapy-associated antitumor activity. Constitutional symptoms related to vector administration consisted of fever and chills only, as has been reported in other clinical trials [30–32]. Other side effects have been observed for blood cells and platelets, liver chemistry and the coagulation profile.

Thrombocytopenia and leukopenia occurred at a maximum around 4 d after vector administration. This early cytopenia could not be linked to the additional administration of gemcitabine as it did not recur after following cycles of gemcitabine administration, and marrow toxicity would not be expected before 8–10 d after treatment. Similar cytotoxic effects have been reported in a trial of sonographically guided intratumoral Adv.RSV-tk injection and intravenous ganciclovir for treatment of colorectal cancer metastatic to the liver [33]. An immediate consumption might be expected and has been suggested because of observations from other trials and animal models. Vector administration to nonhuman primates has demonstrated a saturable and reversible decrease in platelet half-life [34,35]. However, adenoviral vectors have been used to transduce platelets and megakaryocytes efficiently [36,37], and vectors expressing fibroblast growth factor 4 or thrombopoietin can significantly increase platelet counts in animal models [38,39], which strongly suggests that there is no direct inadvertent effect of adenoviral vectors on
**Table 2. Summary of toxicities observed.**

<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional and gastrointestinal symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever (with AGC &gt; 1.0 × 10⁹/L)</td>
<td>0</td>
<td>0</td>
<td>[0] 3 ²</td>
</tr>
<tr>
<td>chills</td>
<td>[0] 1</td>
<td>[0] 1</td>
<td>[0] 1 ²</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>[0] 2 ²</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>[0] 1 ²</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia (muscle pain)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain or cramping</td>
<td>[0] 1</td>
<td>[0] 1</td>
<td>[0] 2 ²</td>
</tr>
<tr>
<td>Chest pain (non-cardiac and non-pleuritic)</td>
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</tr>
<tr>
<td>Hepatic pain</td>
<td>0</td>
<td>0</td>
<td>[0] 1 ²</td>
</tr>
<tr>
<td>Cardiovascular/allergy/infection</td>
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<td>Hepatic</td>
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<tr>
<td>Bilirubin</td>
<td>[1] 2, later 4</td>
<td>[1] 4</td>
<td>[0] 2 ²</td>
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<tr>
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<td>[0] 3</td>
<td>[0] 3</td>
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<td>0</td>
<td>[0] 1</td>
<td>[0] 2</td>
</tr>
</tbody>
</table>

The highest toxicity was documented between days 4 and 6 ( ² the number in brackets represents toxicity grade if CTC criteria were applied before treatment was initiated; * asterixis, encephalopathy or coma; ³ defined by increased fibrin split products or D-dimer; ³ occurring 8 d after treatment and suggested to be related to bacterial cholangitis due to insufficiency of bile stent; ⁴ Thromboplastin time: Grade 0 within normal limits, grade 1 0.75–<1.0 × lower limit of normal; grade 2 0.5–<0.75 × lower limit of normal; grade 3 0.25–<0.5 × lower limit of normal; grade 4 <0.25 × lower limit of normal).

In fact, ex vivo experiments demonstrate that adenovirus does not enhance platelet aggregation upon direct interaction nor does it interfere with ADP, collagen, or epinephrine-induced platelet activation [40]. Hence, the explanation as to why adenoviral vectors did induce this notable drop in platelets as reported in the trials has yet to be determined.

Patients developed laboratory signs of disseminated intravascular coagulation. According to the applied CTC criteria, increased fibrin split products or D-dimers characterize disseminated intravascular coagulation. Additionally, we noted a decline in AT III and thromboplastin time and a prolongation of partial thromboplastin time, all of which accord with activated intravascular coagulation. In spite of the altered laboratory tests and even in combination with the low platelets, none of the patients developed petechiae or other signs of bleeding disorders.
bilirubin returned or nearly returned to pretreatment levels which is comparable to trials utilizing replication-incompetent and replication-selective oncolytic vectors [25,41]. The elevation of liver enzymes started soon after infection and most likely indicated infection and death of hepatocytes due to viral hepatitis. Indeed, increased expression of beta 2-microglobulins and HLA-DR antigens in hepatocytes together with infiltration with CD3(+) CD4(+) and CD8(+) T-lymphocytes, resembling a mild and transient viral hepatitis after receiving adenovirus was found in animal modeling [42]. Severe inflammation of the liver including death of laboratory animals was seen in other models and was dependent on the dosage of vector and on its ability to undergo replicative cycles [21,24].

A possible explanation for most of the observed phenomena could be the initial damage to endothelial and Kupffer cells. Endothelial damage and activation will subsequently activate coagulation and platelet aggregation. Recent data suggest that transduction is different for the three major cell populations composing the liver, Kupffer cells, endothelial cells and hepatocytes, with endothelial and Kupffer cells being more efficiently infected; and even clearance and sequestration of blood from adenoviral vector by Kupffer cells has been described [43,44]. Interaction of viral particles with Kupffer cells could then activate the endothelium by paracrine cytokine effects [45]. Notably, systemic cytokine release through inadvertent targeting of such antigen-presenting cells is probably triggered by the viral capsid proteins.
[46,47], and the depletion of liver from macrophages increases hepatic transgene expression and reduces the immunologic response [44]. Thus, Kupffer and endothelial cell damage might be the primary event triggering a cascade of events involving injury and death of cells, the release of mediators of inflammation and immune activation. In our patients we failed to histologically detect any endothelial damage or coagulation within the smallest vessels of the liver. Endothelial damage itself has been linked to the release of cytokines which, in turn, have been reported from animal models to cause an immediate drop in blood pressure and increase in heart rate [45,48]. In our patients we observed an immediate, but only slight, decrease in blood pressure in only two of three patients, while their heart rate remained constant; no supportive measures had to be taken. However, a severe systemic inflammatory response syndrome, disseminated intravascular coagulation, and multiple organ failure was observed in an 18-year old male participant in a clinical trial which finally led to the death of the patient [28]. The inflammatory response to adenovirus vector administration is not restricted to the liver solely, since a varying level of inflammatory cytokine response was observed with various routes of administration including airway and myocardial administration [49] and cytokine release from mononuclear cells has been observed ex vivo [46].

We saw a major improvement in a patient receiving $7.5 \times 10^{12}$ PFU of rAd/p53 and stable disease in a patient receiving $2.5 \times 10^{12}$ PFU on days 2, 3 and 23, 24 in combination with gemcitabine chemotherapy. Clinical trials using hepatic artery, intravenous or intratumoral infusion as the route of administration have reported antitumor activity and mild toxicity [25,26,50]. In a previous trial utilizing endoscopic ultrasound-guided transgastric delivery of ONYX-015 into unresectable pancreatic carcinomas 10 of 21 patients responded to treatment in combination with gemcitabine [51], and 17 out of 23 patients had mixed tumor responses after CT-guided injection of ONYX-015 [52]. In a further study of administration of $4 \times 10^{7}$ to $4 \times 10^{11}$ viral particles of a TNF-z expressing adenovector (TNFerade) that included patients with pancreatic carcinoma, a tumor response was documented in 3 out of 6 patients [53]. Only limited data is available concerning long term survival in trials utilizing p53 transfer. However, a median survival of 12 to 13 months compares favorably to a 5-month survival seen with palliative radiotherapy or paclitaxel failure in heavily pretreated patients with recurrent ovarian cancer [54].

To date, there is still limited information available on clinical trials utilizing adenoviral gene transfer strategies for metastatic pancreatic carcinoma, and few of the strategies explored in animal modelling have been evaluated for safety and efficacy in the treatment of the human disease. In summary, our study involving three patients who received a combination therapy of viral gene transfer and chemotherapy shows some potential in temporarily controlling and even diminishing tumor burden in one patient. The side effects and toxicity observed in our trial were mild and well tolerated. Further trials are warranted in an effort to improve the treatment and life expectancy of patients suffering from fatal diseases such as pancreatic carcinoma.

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References


