Personalized medicine – p53 gene analysis for prediction of response to neoadjuvant therapy in esophageal cancer

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The present review introduces a protocol for a prospective randomized predictive marker clinical trial. The study evaluates the interaction between the proposed predictive marker p53 and response to neoadjuvant chemotherapy in patients with potentially resectable esophageal cancer. This trial is designed to provide “level of evidence I” data, which are a prerequisite for the clinical implementation of a predictive marker. Despite curative resection, the 5-years survival rates of esophageal cancer patients do not exceed 20%. Several phase II and III studies have shown that patients who responded to preoperative chemotherapy had a significantly better survival than patients treated with surgery alone. Up to now, it is not possible to identify the responders before commencing treatment. Eighty-four patients with measurable disease will be enrolled in the pANCHO trial. After testing the marker genotype (p53 normal versus p53 mutant), patients will be randomly assigned to receive two different chemotherapies – 5FU/Cisplatin or Docetaxel. All patients will be rendered to subsequent surgery and as a primary endpoint response to neoadjuvant treatment will be evaluated. The pANCHO trial is a nationwide academic initiative. The 13 affiliated investigational centres recruited 70% of estimated patients within one year. Patients enrolled in the pANCHO trial benefit from the standardized diagnostic and therapeutic procedures. The study is supposed to identify the need for new guidelines for response assessment in neoadjuvant treated patients. Marker specific results are awaiting autumn 2009 and could be relevant to the choice of therapy in esophageal cancer.

Keywords: Individualized cancer therapy, esophageal cancer, p53, neoadjuvant therapy, predictive marker trial, response prediction, pANCHO

Introduction

Implementation of a predictive marker in the treatment of esophageal cancer

Esophageal cancer represents one of the eight most common cancers worldwide and showed a dramatic increase in incidence, especially for the adenocarcinoma type, during the past years.

Esophagectomy is considered as a standard therapy for patients with resectable esophageal cancer but only few patients are cured. Curative resection may be compromised due to the proximity of the esophagus to the vital mediastinal structures. The early lymphatic and haematogenous spread are additional limitations of cure.

The 5-year survival rates range between 15 and 25% and postoperative radio- and/or chemotherapy did not prove to increase survival [1, 2].

In an attempt to be effective in the prevention of systemic spread and to improve the chance for complete resection by downsizing, neoadjuvant treatment strategies were investigated in clinical trials during the past decade [3–6].

Meta-analyses of several randomized controlled phase III trials comparing neoadjuvant chemotherapy or chemoradiation followed by surgery to surgery alone produced conflicting results for the overall survival benefit [7]. Various neoadjuvant protocols experienced limitations based on toxicity and compliance.

However, those patients who experience complete pathological remission consistently show a dramatic survival benefit and an enhanced chance for cure [3–6].

Identification of responders before commencing neoadjuvant therapy appears to be a promising strategy to achieve a major progress in the treatment of esophageal cancer.

This strategy emphasizes the identification of molecular tumour markers that could be used to predict response or resistance to chemotherapy [8].

The introduced pANCHO trial aims to assess whether p53, as a single genetic marker, can be used to choose an effective treatment for the individual esophageal cancer patient.
Materials and methods

p53 as a predictive marker for chemotherapy

It is generally accepted that cytotoxicity of drugs interacting with DNA is not mediated through DNA damage itself through the induction of apoptosis. As DNA damage is the strongest trigger for the activation of the p53 gene and as the p53 gene crucially controls the apoptotic pathway, the presence of wild-type p53 in a tumour cell seems to be a prerequisite for successful cancer treatment with drugs making use of the apoptotic pathway [9–12].

A number of retrospective clinical studies showed a strong relationship between the presence of a normal p53 gene and response to DNA damaging agents. Response to standard regimens like cisplatin/ifosfamid, fluorouracil/epirubicin/cyclophosphamide, cisplatin/5-FU as well as radiation proved to be significantly related to a normal p53 gene in non-small-cell lung cancer, breast, oesophageal and rectal cancer patients [13–16].

Rationale for the pANCHO trial design

The main objective of a predictive marker trial is to test the hypothesis that the marker is useful for guidance in choosing an optimal treatment.

Since our study is focused on testing the predictive relevance of the p53 genotype for the choice of therapy, the design of the trial is devoted to this goal. The chosen design follows the concept of Marker by Treatment Interaction Design [17] (Fig. 1).

For the application of this powerful design, the following qualifications have to be fulfilled:
- The status of the marker splits the whole population into two distinct groups (p53 normal versus p53 mutant).
- For each group a different therapy appears to be effective.

Thus, the aim of the study is neither to show that a specific treatment is effective nor to show that a treatment is overall superior to another treatment.

The focus of the pANCHO trial is the validation of the predictive marker p53. Therefore, we want to determine, whether the treatment effect seen in one group differs significantly from the treatment effect seen in the other group by a formal statistical test for the interaction between marker status and treatment assignment.

The marker prevalence (p53 mutation frequency) was tested in a pilot cohort of oesophageal cancer patients. Marker analysis was performed using complete direct DNA sequencing of the p53 gene, which represents the golden standard of p53 analysis.

The pilot study also provided information on the predictive effect of p53 relative to two different chemotherapies for oesophageal cancer [18]. The results of this pilot were the basis for proposing the hypothesis and for considering the sample size of the pANCHO trial.

Results

pANCHO – study details

pANCHO is a nationwide Austrian trial for potentially resectable oesophageal cancer patients. The prospective randomized study is an academic driven trial sponsored by the Austrian Society for Surgical Oncology (ACO/ASSO).

Study ID: ASSO OE-1
EudraCT Number: 2006-006647-31
ClinicalTrials.gov. identifier NCT00525200
**Study chair:** Daniela Kandioler, ASSO Representative, p53 Research Head, MUW Dept. Surgery  
**Study directors:** Johannes Zacherl, MUW Dept. Surgery, Michael Hejna, MUW Dept. Oncology

**pANCHO – trial design**

![Trial Design Diagram](image)

**Fig. 3:** Patients who meet the eligibility criteria will be assigned to receive either a combination therapy with 5-Fluorouracil and Cisplatin (Arm A), or a single-agent therapy with Docetaxel (Arm B). After testing the marker genotype (normal or mutant p53) patients will be stratified according to the histological subtype (adenocarcinoma or squamous cell carcinoma) and will be randomly assigned to receive three cycles of either Cisplatin/5 Fluorouracil or Docetaxel as neoadjuvant therapy. (Chemotherapy dosage: Cisplatin 80 mg/m² day 1 and 5-Fluorouracil 1000 mg/m² days 1-5; q21, 3 cycles. Docetaxel 75 mg/m² day 1; q21, 3 cycles). All patients will be rendered to subsequent surgery in order to assess and compare both clinical and pathological response.

**Tab. 1: Patients eligibility criteria**

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<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>Histological verification of oesophageal cancer.</td>
<td>Inoperability (technical or functional)</td>
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<tr>
<td>Presence of T2, T3, T4 or T1N1 disease and M0 (potentially respectable)</td>
<td>Clinical stage cT1N0 or any tumour stage with M1</td>
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<tr>
<td>Males and females, age &gt;18 to 75 years or elder patients with WHO performance status 1</td>
<td>Treatment within the last 6 months with any of the investigational drugs</td>
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<tr>
<td>Concurrent administration of any other tumour therapy, including radiotherapy, cytotoxic chemotherapy, immunotherapy, molecular target therapy, gene therapy</td>
<td>Serious concomitant disorders that would compromise the safety of the patient or compromise the patient’s ability to complete the study, at the discretion of the investigator</td>
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<tr>
<td>Second primary malignancy that is clinically detectable within the last 5 years from the time of consideration for study enrolment</td>
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**pANCHO – operational procedures**

1. After having obtained written informed consent, tumour biopsies of eligible patients are sent to the study centre (MUW). Patients receive a Study ID to make themselves anonymous.

2. Routinely paraffin embedded tumour biopsies are used for complete sequence analysis of the p53 gene. The gene analysis for the study is performed centrally in the certified laboratory of the p53 research group ([www.p53.at](http://www.p53.at)).

3. The information on the histological tumour type is required for the stratification to ensure that adenocarcinomas and squamous cell carcinomas are equally distributed in the treatment arms. Permuted block randomization is used to allocate patients to the two treatment arms and to ensure that the two different chemotherapies will be equally distributed between patients with p53 mutated and normal tumours. Patients and investigators are
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informed which chemotherapy the patient has been randomized for, while the predictive marker information (p53 genotype) is blinded to both of them.

(4) After three cycles of chemotherapy resting is performed, the patients are subjected to surgery.

(5) p53 sequence analysis is repeated with paraffin embedded tumour material from the surgical specimens.

Primary outcome measures (time of availability)

- Pathological tumour response to neoadjuvant treatment in relation to p53 genotype (12 weeks after inclusion)
- Complete pathohistological response rate and relation to p53 genotype (12 weeks)

Secondary outcome measures (time of availability)

- Complete tumour resection rate (12 weeks)
- Perioperative morbidity and mortality (16 weeks)
- Disease free and overall survival (2 years)

Conclusions

The pANCHO trial is an academic driven clinical predictive marker trial, which proved to be extremely successful in recruiting oesophageal cancer patients in Austria. The perfect interdisciplinary cooperation between surgical and medical oncologists, radiologists and pathologists encouraged by the innovative protocol resulted in the recruitment of 70% of patients in the 13 affiliated centres within the first year. Simple study logistics as well as the close cooperation between the study management and study coordination allow immediate data recruitment.

The gene marker analysis is performed centrally. Pathological and radiological response after neoadjuvant therapy will be assessed and compared by two internationally staffed response assessment boards blinded to the marker information. These boards are supposed to identify the need for new guidelines for response assessment for neoadjuvantly treated patients.

The operational procedures of the pANCHO trial are qualified to standardize the treatment of oesophageal cancer in Austria. Marker specific results are awaiting autumn 2009 and could be relevant to the choice of therapy in oesophageal cancer.

Take home message

The pANCHO trial tests for the first time the hypothesis that p53 is predictive for response to neoadjuvant chemotherapy in oesophageal cancer patients and could be relevant to the choice of therapy.

The pANCHO trial was started in Austria in June 2007; Based on the actual accrual of 70% of patients, end of study is predicted for January 2009. Results are awaiting autumn 2009 and will be presented at the Annual meeting of the ACO ASSO 2009 in St. Wolfgang, Salzkammergut (Fig. 4).

Acknowledgements

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www.p53.at
www.aco-asso.at
References


