The development of new treatment strategies for oesophageal cancer

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Citation for published version (APA):
Epilogue
INTRODUCTION

To improve the clinical outcome of patients with oesophageal cancer, insight in the premalignant stage (also called Barrett's oesophagus) and the subsequent metaplasia-dysplasia-adenocarcinoma sequence is important, as is described in this thesis. Preoperative knowledge of prognostic factors (i.e. depth of invasion, lymph node involvement and distant metastases) is necessary to identify patients eligible for surgery, but clearly new prognostic markers and novel adjuvant treatment strategies are needed. Knowledge of the pathways involved in the malignant degeneration might lead to early detection with increased overall survival and the development of more specific treatment strategies for invasive cancer.

With the completion of the human genome project, almost one hundred thousand genes and their accompanying proteins have been identified. Although with this genomics project, the DNA origin of most proteins is known, the function of the majority of enzymes remains largely unknown. Especially identifying enzymes involved in the malignant degeneration of normal tissues will be the next challenging goal. So far, in our institute the molecular analysis of oesophageal cancer has mainly focused on the prognostic significance of alterations in single candidate genes like cyclooxygenase-2 (COX-2) and the oncogenic form of the normal receptor tyrosine kinase c-erbB-2. These single candidate genes do not have sufficient prognostic power in the clinical setting to justify clinical implementation.

However, recent advances in molecular biology have resulted in the so-called DNA expression microarray technology. This method provides detailed gene expression profiles of individual cancer tissues and has been recently introduced in the context of tumour staging in cancer research. The results can be used to help identify alterations common to all tumours as well as signatory mRNA expression profiles unique to a subcategory of cancers. In breast and prostate cancer such mRNA expression profiles of the cancer tissue have proved to be a more powerful predictor of outcome of disease than standard clinical and histological criteria. For oesophageal adenocarcinoma, this technique will contribute significantly in the attempt to unravel more of the Barrett's metaplasia-dysplasia-adenocarcinoma sequence. To make optimal use of this development, tissue specimens available for research are of crucial importance. Therefore, one of the targets in current research is the adequate storage of fresh frozen patient-material to create a 'tissue-bank' in combination with prospectively collected patient follow-up data.
DEVELOPMENT OF NOVEL DIAGNOSTIC MODALITIES

Endoscopic imaging
Detection of high-grade dysplasia (HGD) or early carcinoma in a Barrett's oesophagus can be difficult due to heterogeneity of the Barrett's epithelium that cannot be discriminated with standard endoscopy. The detection of these early lesions by random biopsies is hampered by sampling error, and the intra- and interobserver variation of histological classification of observed abnormalities. The presence of genetic alterations in metaplastic and dysplastic Barrett's epithelium might be used in the future surveillance of patients with Barrett's oesophagus since these molecular markers might identify a subset of patients with an increased risk of malignant degeneration. At this moment, a large project in our institute is the addition of brush-cytology in combination with fluorescence-in-situ hybridisation (FISH) to the surveillance program of patients with a Barrett's oesophagus. This technique can be used to detect genetic alterations like tetraploidy and loss of tumour suppressor genes (p53 or p16). Because the entire Barrett's segment is brushed instead of taking random biopsies, the sampling error might be decreased.

In addition, several new endoscopic techniques are being studied for their contribution to optimize detection of early lesions in a Barrett's oesophagus. Examples are high-resolution endoscopy, chromoendoscopy, fluorescence endoscopy and optical coherence tomography, but so far methylene blue staining and magnification chromoendoscopy are the only techniques that have shown to increase the detection rate of HGD. At this moment there is a randomized controlled trial at the department of gastroenterology analysing the adjuvant value of light induced fluorescence endoscopy (LIFE) which uses standard white-light endoscopy in combination with monochromatic blue-light for LIFE.

Positron Emission Tomography imaging
There is also need for more accurate staging of more advanced carcinomas to select those patients who will benefit from potentially curable surgery while avoiding unnecessary operations in patients with locally irresectable tumours or distant metastases. The relatively low accuracy in determining surgical curability of the current staging methods (CT-scan and endoscopic ultrasonography) indicates the need for a different approach. Whole body positron emission tomography (PET) uses radioactive metabolites to detect metabolic derangements in malignant tissues. This technique uses a one
step single staging method with metabolic tracers such as 18 F-Fluorodeoxyglucose (FDG). The diagnostic value of FDG-PET for improving preoperative staging of oesophageal cancer (especially detection of unsuspected non-regional lymphatic or haematogenic disease) is currently analysed in our institute.12

DEVELOPMENT OF NOVEL THERAPEUTIC APPROACHES

Local endoscopic treatment strategies
Endoscopic treatment of patients with HGD and/or early cancer of the mucosa in a Barrett’s oesophagus by mucosal resection and/or tissue ablation techniques seems a promising alternative to surgical resection.13 The limited invasiveness in comparison to surgical resection results in decreased procedure related mortality and morbidity and the preservation of a functional oesophagus is probably associated with an increased quality of life. Recent studies demonstrated that these techniques are feasible and safe14,15, but long-term follow-up results have to be awaited before they can be considered as gold standard. Currently, patients in our institute with HGD or early adenocarcinoma of the oesophagus are treated according to the protocol as described in this thesis. Patients with a suspected early lesion not infiltrating the submucosa as diagnosed by endoscopic ultrasonography (EUS), undergo an endoscopic mucosal resection (EMR) for histological verification. In case of a radically resected HGD or an intramucosal carcinoma smaller than 3 cm, with good or moderate differentiation grade and no lymph-angio invasion, the EMR is considered therapeutic and the patient is followed strictly for the potential development of new lesions. When the lateral resection margin shows HGD or other areas of HGD are identified, the patient is treated with 1-2 sessions of adjuvant photodynamic therapy (PDT). If this treatment results in complete eradication of HGD, the patient is considered in remission and placed under stringent follow-up. However, if there is still HGD or invasive carcinoma after PDT, surgical resection of the oesophagus is advocated.

Pharmacodynamic strategies
First attempts in the development of specifically targeted chemotherapeutic treatment strategies for oesophageal adenocarcinoma have been made with the development of EGFR inhibitors and selective COX-2 inhibitors. The rationale of the latter approach is described in this thesis.16,17 Several large clinical trials with selective COX-2 inhibitors for the prevention of malignant
degeneration of a Barrett's oesophagus or selective COX-2 inhibitors as (neo-) adjuvant therapy for Barrett's cancer are currently being performed. In our institute, the value of celecoxib as neo-adjuvant therapy in patients with an adenocarcinoma of the oesophagus or gastric cardia is investigated by analysing its effect on various tumour markers. With this approach we also hope to increase the knowledge of the role of COX-2 in the development of oesophageal adenocarcinoma.

To improve the clinical application of the new generation of targeted chemotherapeutic drugs, it has been suggested that combination therapies might increase their chemopreventive or adjuvant effect. A remarkable phenomenon in this context of pharmacodynamic treatment strategies is the finding that newly developed cytostatic chemotherapeutics are often synergistic with the traditional cytotoxic chemo- and radiotherapy. Various studies suggest that specific inhibition of proliferation pathways increases the sensitivity of cancer cells for apoptosis. Therefore, future research has to focus on therapies with combinations of novel therapeutic agents (e.g. drugs inhibiting proliferation pathways and/or inhibiting angiogenesis) and combination strategies of cytostatic and cytotoxic chemotherapies.

Gene therapy

Gene therapy has evolved as a new therapeutic strategy with great potential for various malignancies. So far, most of the research is still in a preclinical phase. The first steps in the development of gene therapy for oesophageal cancer are described in this thesis. As with all forms of cancer gene therapy, the main problem in developing this new therapeutic approach for oesophageal malignancies is to optimise gene delivery in order to maximize the proportion of successfully transduced tumour cells while increasing selective transduction to spare normal cells.

Several targeting approaches to increase the efficiency and/or selectivity of gene delivering vectors for oesophageal cancer have been analysed with promising in vitro results. Examples are genetic targeting with insertion of an RGD peptide into the fiber knob to skip binding of the virus to the CAR-receptor, and the development of conditionally replicating adenoviruses (CRAds) to increase gene transfer efficiency. To increase tumour selectivity, transcriprional targeting strategies (e.g. placing the vector under control of a tumour specific promoter) are analysed. Unfortunately, most currently performed clinical trials show disappointing results and obviously a lot of research is needed before gene therapy can play a significant role in the management of oesophageal cancer. At this moment, the focus of this research is on developing new experimental models as well as improving
gene delivering vectors or novel therapeutic genes that can have a synergistic effect with current adjuvant therapies. Another interesting field of research is the development of fiber chimeric adenoviruses. There are at least 50 serotypes of human adenoviruses, of which the serotypes Ad2 and Ad5 (subgroup C) are most frequently used. Since it has been suggested that other serotypes have different tropism for various tissues with distinct cellular receptors, this has led to the construction of adenoviruses with chimeric fibers. At this moment the serotypes of subgroup B (e.g. Ad5/fiber 16 and Ad5/fiber 35), which have been demonstrated to have a CAR independent transfection and show increased infectivity in pancreatic carcinoma cell lines, are analysed at the laboratory of the AMC Liver Center. Although it is unlikely that cancer gene therapy will replace the conventional methods of treatment, selective and efficient vectors might be used as monotherapy for specific patient groups or as (neo-) adjuvant therapy improving the chance for cure in patients with oesophageal cancer in the future.

CONCLUSIONS

There is need for increased understanding of the molecular biology of Barrett’s oesophagus and oesophageal adenocarcinoma to improve diagnosis, therapy, and prognosis for patients with this aggressive disease. Recently developed microarray technology and proteomics will probably contribute significantly in the attempt to unravel more of the Barrett’s metaplasia-dysplasia-adenocarcinoma sequence. It is expected that this knowledge will lead to new target-specific treatment strategies with or without conventional aspecific chemo- and radiotherapy in the near future. One of the problems in this area is the choice of target enzymes to be inhibited since it might be hypothesized that inhibition of various pathways will lead to selection of resistant tumour cells with more aggressive behaviour. Obviously, a lot of research has to be done in the field of diagnosis and treatment of oesophageal malignancies. The studies described in this thesis have attempted to address some of these issues and hopefully it will become clear in the next few years if better targeted treatment strategies will lead to improved clinical outcomes for patients with oesophageal cancer.
REFERENCES


