Predictive Factors in the Neoadjuvant Chemoradiotherapy of Gastrointestinal Tumors

PhD Thesis

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1. INTRODUCTION

Neoadjuvant chemoradiotherapy (CRT) followed by surgery is a widely accepted treatment in gastrointestinal tumors such as loco-regionally advanced esophageal and rectal cancer. From theoretical perspective neoadjuvant CRT offers several advantages compared to postoperative treatment. Better oxygenation of the tumor area leads to increased radiosensitivity enhancing radiation response. Downsizing of the tumor may facilitate optimal surgical removal, which may enable function preservation. The combination of radiation and systemic agents decreases tumor seeding, consequently may improve local and distant control rates. In clinical practice patients can tolerate preoperative treatment better, due to less acute toxicity and lack of postoperative complications. Moreover, radiotherapy target volume for treatment planning is easier to define because of visible tumor mass. One of the main disadvantages of the neoadjuvant treatment strategy is the potential overtreatment of patients with early disease. In addition, not all tumors respond to neoadjuvant CRT, thus non-responding patients may progress during the preoperative therapy and suffer from unnecessary toxicity. The ultimate response to CRT is determined by the quality of treatment, as well as by the genetic make-up of the tumor and the various biochemical pathways implicated in chemoradiosensitivity. Understanding the biology of the disease and pretreatment identification of molecular markers predicting therapeutic response would be invaluable in individualizing patient treatments.

2. THESIS

The aim of this study was to investigate certain molecular-biological markers which characterize the two major cell death pathways as possible clinically useful predictors of response to neoadjuvant CRT for esophageal and rectal cancer. The main objectives of my research were the following:

1. to assess the efficacy and tolerability of the neoadjuvant chemoradiotherapy regimen used in treatment of loco-regionally advanced squamous cell esophageal carcinoma

2. to determine a correlation between the expression of heat shock proteins (HSP90 and HSP16.2) and the clinical or pathological response to neoadjuvant CRT in esophageal cancer

3. to determine a correlation between the Bax/Bcl2 ratio, representing the apoptotic route of cell death, and the clinical or pathological response to neoadjuvant CRT in esophageal cancer

4. to determine a correlation between SOUL implicated in necrotic cell death and the clinical or pathological response to neoadjuvant CRT in esophageal cancer

5. to identify, whether there is any difference in tumor-related protein expression of squamous cell carcinomas arising in the middle or in the upper third of esophagus

6. to evaluate efficacy of neoadjuvant CRT regarding pathological response in loco-regionally advanced rectal cancer and to assess the impact of patient/therapy-related clinical factors on tumor response

7. to identify, whether the expression of heat shock proteins (HSP90 and Hsp16.2) are correlated with histopathological response after neoadjuvant therapy of rectal cancer

8. to identify, whether expression of p-AKt has any influence on histopathological response after neoadjuvant therapy of rectal cancer

9. to evaluate the impact of GHRH-R expression on histopathological response after neoadjuvant therapy of rectal cancer

10. to evaluate the impact of necrosis-inducing heme-binding protein 2 (SOUL) expression on histopathological response after neoadjuvant therapy of rectal cancer to identify one or more tumor-associated proteins as independent predictive markers of the response of individual rectal tumors to neoadjuvant CRT

11. to identify one or more tumor-associated proteins as independent predictive markers of the response of individual rectal tumors to neoadjuvant CRT

3. MATERIALS AND METHODS

3.1. Materials and Methods in Esophageal Study

Patients and tumor specimens

Twenty patients with esophageal cancer, candidates for NRCT, were enrolled in the study between 2005 and 2006. All the patients had squamous-cell cancer, with stages cT3-4, cN0-1, cM0, located in the upper two-thirds of the esophagus. The staging procedures included endoscopy with biopsy, endoscopic ultrasound, computed tomography (CT) scan of chest and abdomen and bronchoscopy. From each patient one biopsy was taken from the tumor and one biopsy from the intact part of the esophagus to serve as control. The biopsy from the tumor was divided into two parts. One tumor sample and the normal tissue sample were immediately frozen in liquid nitrogen and the other tumor sample was formalin-fixed for pathological examination. The biochemical examinations were carried out on fresh frozen samples. The patients then received external-beam radiotherapy (total of 36 Gy, fraction dose: 1.8 Gy) and concomitant chemotherapy during the first week of irradiation: cisplatin (100 mg/m^2 intravenously on day 1) and 5-fluorouracil (1000 mg/m^2/day, continuous intravenous infusion through days 1-5). Four weeks after the completion of RCT, the clinical response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST). Six to nine weeks after the neoadjuvant therapy if there was no evidence of disease progression, the patients underwent definitive surgical resection. Pathological response to treatment was determined by the histological evaluation of the resected specimen. Side-effects were documented in conformity with the Common Terminology Criteria for Adverse Events, Version 3.0.

Immunoblot analysis.

The tissue specimens were homogenized, then centrifuged for 10 minutes. Isolation of the cytosol and nuclear fractions was carried out by standard laboratory protocols described previously. The samples were equalized to 1 mg/ml total protein concentration using Biuret's method and subjected to SDS-PAGE. The proteins were separated and then transferred to nitrocellulose membranes. The membranes were exposed to the following primary antibodies: anti-Hsp 16.2, anti-SOUL, anti-Hsp 90, anti-Bax and anti-Bcl-2. Appropriate horseradish peroxidase-conjugated secondary antibodies were used and peroxidase labeling was visualized with enhanced chemiluminescence (ECL) using an ECL Western blotting detection system. The developed films were scanned, and the pixel volumes of the bands were determined using NIH Image J software. All the experiments were repeated four times.

Statistical analysis

Statistical analysis was performed by analysis of variance followed by Student's *t*-test and the Mann-Whitney *U*-test. Statistical significance was set at $p<0.05$. The analyses were performed using the statistical software SPSS for Windows.

3.2. Materials and Methods in Rectal Study

Patients, Pre-treatment and Posttreatment

Sixty nine consecutive patients with median age of 59 years (range 34-78), were treated for rectal adenocarcinoma with neoadjuvant CRT between January 2005 and December 2006. All the patients had locally advanced tumors (cT3/T4 and /or cN+ and cM0). Preteatment workup consisted of digital rectal examination, sigmoidoscopy, biopsy, abdomino-pelvic CT, pelvic MRI, chest x-ray or CT. In all cases 3D planned conformal radiotherapy was carried out with belly board in prone position, with 18 MV photons. Primary tumor as well as lymph nodes at risk were covered with 3 irradiation fields and received 45 Gy in 25 fractions over a period of 5 weeks. As a concomitant chemotherapy, 500 mg/m^2 of 5-Fluorouracil continuous infusion and 30 mg/m^2 Folic acid bolus on days 1-5 of 1st and 5th weeks of radiotherapy was administered. Four weeks after the completion of CRT, patients were re-staged and definitive surgical resection was performed six to nine weeks after neoadjuvant therapy in 64 cases.

Histopathological Evaluation

Pathological response to neoadjuvant treatment was determined by the histological evaluation of the resected specimens using rectal radiotherapy grading system adapted from Mandard et al. This five point tumor regression grading (TRG) is based on the presence of residual tumor cells and the extent of fibrosis and consists of the following: TRG 1 (complete regression) is defined as the absence of residual tumor and fibrosis extending through the different layers of the rectal wall, TRG2 is characterized by the presence of rare residual tumor cells scattered throughout the fibrosis, TRG3 shows an increase in the number of residual tumor cells, but the fibrosis still predominates, TRG4 demonstrates residual tumor outgrowing the fibrosis and TRG5 is characterized by the absence of any tumor regression. In accordance with previous studies in order to simplify the statistical analysis, the TRG was combined into two groups: good responders comprising TRG1-2 and poor responders consisting of TRG 3- 5.

Immunohistochemistry

Sections from the pretreatment tumor tissue samples were fixed in formalin and embedded in paraffin. Subsequently, they were incubated with the following primary antibodies: self-developed anti-Hsp 16.2 and anti-SOUL polyclonal primary antibodies, GHRH-R primary antibody, p-AKT and Hsp90 primary antibodies. Immunohistochemical staining was carried out and the staining intensity was recorded semiquantitatively as mild (+), moderate (++) or strong (+++). All slides were assessed by the same experienced pathologist blinded to clinico-pathological data.

Statistical Analysis

All statistical analyses were carried out using SPSS 16.0 statistical program. Univariate chi-square test was used to compare clinical parameters and biological markers for tumor regression grade. To increase the number of patient per group, the categories of the various variables were combined for these analyses: age over 60 years vs. below 60 years, cT2 vs. cT3 vs. cT4, cN0 vs. cN1-2, distance from the anal verge less than 5 cm vs. between 5 and 10 cm vs more than 10 cm, time to surgery within 7 weeks vs. over 7 weeks. For statistical testing intensity values of immunohistochemistry were dichotomised into low (0, +) and high (++, +++) intensity categories. All parameters were analysed afterwards in a logistic regression multivariate analysis. A p value of less than 0.05 was considered statistically significant.

4. RESULTS

4.1. Results in Esophageal study

Clinical outcome.

A 65% clinical response rate was found. One patient had complete remission (5%), 12 patients had partial remission (60%), 5 patients had stable disease (25%), 1 patient had progressive disease (5%) and 1 patient died during the treatment (5%). The patients with complete or partial remission underwent definitive surgery. The following histological response was observed: no residual tumor tissue in 2 patients (10%), down-staging of the tumor size (T) or lymph node involvement (N) in 6 (30%) and 5 (25%) cases, respectively. Complete (R0) resection was possible in 9 cases (70%) and no perioperative mortality occurred. Grade 3 or 4 gastrointestinal (30%), hematological (15%) and pulmonary (15%) side-effects occurred, one patient (5%) died due to severe sepsis.

Detection of possible new markers by Western-blot.

All twenty squamous-cell esophageal cancer and corresponding normal esophageal tissue samples were examined by Western-blot. The tumor samples from the patients with no clinical response contained approximately double the level of Hsp 90 and Hsp 16.2, significantly higher than responding tumors (p=0.049 and p=0.019 respectively). They also expressed SOUL at a higher level and had a lower Bax/Bcl-2 ratio than those with good clinical response, but these results were not significant (p=0.247 and p=0.883). The results of the pathological examination were similar to the clinical results. The tumors with no histological response expressed twice as much Hsp90 (p=0.0005) and Hsp16.2 (p=0.002) and 1.5 times more SOUL (p=0.218) than the responders. On the other hand, a lower Bax/Bcl-2 ratio was seen in the non-responders compared to the responders, but as SOUL this result was not significant (p=0.499). Particularly interesting results were observed when the samples were analyzed according to the tumor location. The upper tract tumors expressed the Hsp proteins in significantly lower quantities than the tumors located in the lower-third of the esophagus (Hsp90 upper *vs.* middle-third p=0.006 and Hsp16.2 upper *vs.* middle-third p=0.012). The SOUL protein was also expressed in significantly smaller quantities in the upper-third of the esophagus (p=0.047). Although the Bax/Bcl-2 ratio seemed to be lower in the middle-third tumors, the difference was not significant (p>0.05).

4.2. Results in Rectal Study

Histopathological Response to Neoadjuvant CRT

Curative resection was performed in 64 (92 %) cases. The surgical intervention was a low anterior resection in 49 cases (70%) or abdomino-perineal resection in 15 cases (21%), with R0 resection rate of 90%. Pathological evaluation of response to preoperative CRT in resected rectum specimens revealed complete response (TRG1) in 11 of 64 cases (17%) and significant response (TRG2) in 20 of 64 cases (31%). Hence good responders encompassing TRG1 and TRG2 categories account for 48% of patients, while poor responders including TRG3 for 19 cases (30%), TRG4 for 12 cases (19%) and TRG5 for 2 cases (3%) represented the remaining 52% of the patients.

Protein Expression in Pre-treatment Biopsy Specimens

Immunohistochemical evaluation of the pre-treatment biopsy specimens showed high intensity staining (++, +++) for SOUL, Hsp 16.2, Hsp90 and for GHRH-R in 67%, 61%, 58% and 25% of the cases, respectively. High intensity p-Akt staining was found in all the rectum biopsy specimens.

Association Between Pre-treatment Clinical Data and Histopathological Response to CRT

None of the pre-treatment clinical characteristics except the elapsed time interval between the end of neoadjuvant therapy and surgery was found to be statistically related to histopathological response. The patients who were operated on 7 weeks or more after CRT ended, had a significantly higher chance of showing a good response to neoadjuvant treatment, than those who underwent surgery within 7 weeks (63% versus 37%, p=0.041) following CRT. Univariate analysis of the correlation between other clinical parameters including age, sex, distance from anal verge, pre-treatment cT or cN and tumor regression grade revealed no statistically significant association.

Association between Protein Expression and Histopathological Response to CRT

Among the markers evaluated in pre-treatment biopsy specimens, SOUL, Hsp16.2 and p-Akt staining did not show a significant association with tumor regression grade. However, high levels of Hsp90 and GHRH-R expression in the pre-treatment tumor biopsies were significantly correlated with poor histopathological response (p=0.00002, p=0.00006 respectively). Multivariate analyses confirmed that the association of GHRH-R and Hsp90 expression with the therapeutic response was significant (for pGHRH odds ratio, 0.198; 95% confidence interval, 0.042-0.941; p<0.05 and for Hsp90 odds ratio, 0.218; 95% confidence interval, 0.074-0.647; p<0.001) after data was adjusted to account for the clinicopathological parameters and expression of the other markers.

5. CONCLUSIONS

In conclusion, our results suggest, in line with previous studies, that response to neoadjuvant therapy depends on the treatment protocol including the radiation dose and time between CRT and operation as well as on the biological features of tumor. The identification of biomarkers predicting the responses would allow more effective and individualized treatment.

1. In the present retrospective study of esophageal cancer the rate of complete responses achieved with neoadjuvant chemoradiotherapy was lower than pCR rates reported in the literature, which implies a need for escalation of radiation dose. However, the serious and fatal side effects related to CRT scheme indicate that any intensification of therapy requires thorough selection of patients.

2. In tumor samples from esophageal cancer patients with no clinical or pathological response to neoadjuvant CRT significantly higher levels of HSP90 and HSP16. 2 expression were detectable than in responding tumors, indicating the role of heat shock proteins in resistance against chemo-radiotherapy.

3. Our data demonstrate no significant association between the response of esophageal tumors to CRT and BAX/Bcl2 ratio representing the apoptotic form of cell death.

4. The present study did not find a significant association between the response of esophageal tumors to CRT and the expression of SOUL, a protein implicated in necrotic cell death.

5. Upper tract esophageal tumors expressed HSP proteins and SOUL protein in significantly lower quantities than middle-third tumors, which may contribute to their different sensitivity to CRT.

6. The current investigation indicates that pre-treatment clinical parameters do not influence the chemo-radiosensitivity of rectal cancer, whereas the time interval longer than 7 weeks between neoadjuvant CRT and operation is associated with better tumor response.

7. As regards cytoprotective heat shock proteins, the level of immunhistochemical staining of Hsp 16.2 was not related to tumor regression, whereas the expression of HSP90 was significantly correlated with poor histopathological response to CRT for rectal cancer.

8. The results of our study do not support the view that the expression of anti-apoptotic p-AKT has any influence on histopathological response to CRT for rectal adenocarcinomas.

9. A significant correlation between the expression of GHRH-R and poor histopathological response to neoadjuvant CRT for rectal cancer was demonstrated.

10. In the present study the level of immunhistochemical staining of necrosis-facilitating SOUL was not related to histopathological regression of rectal cancer after neoadjuvant CRT.

11. Our data indicate that GHRH-R and Hsp90 may serve as pretreatment predictors of tumor regression to neoadjuvant CRT in rectal cancer. Moreover GHRH-R and Hsp90 hold promise of providing novel therapeutic options for poor responder patients. Nevertheless, before any clinical implications can be drawn, further studies are warranted to confirm our results.

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