CA 15-3 is a predictive and prognostic biomarker in patients with metastasized breast cancer undergoing Selective Internal Radiation Therapy

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Introduction

The prognosis for patients with hepatic metastasized breast cancer is rather poor with a median survival of 1 – 14 months and only a few patients benefit from surgical resection [1]. Selective Internal Radiation Therapy (SIRT), a locoregional anticancer therapy for disseminated and extensive liver metastases, offers new treatment options. The tumor is damaged directly as radiating microspheres containing Yttrium are administered through the hepatic artery supplying the tumor tissue, while the healthy radiation-sensitive liver tissue is relatively spared as its blood supply is secured through the portal vein [2]. Initially, SIRT was used mainly in patients with liver metastases of colorectal cancer, but several recent studies have shown promising results for hepatic metastases of breast cancer when treated with SIRT [3]. To avoid unnecessary treatment and collateral side effects in individual patient management, pretherapeutic markers indicating therapy response and prognosis are needed for the stratification of patients for SIRT [4]. In addition, changes in individual markers appearing already in the first days after SIRT reflect therapy response and prognosis and are thus valuable for early treatment adaptation [5]. For both purposes, circulating biochemical markers in the blood are the preferred candidates as they are related to cancer biology as well as therapy efficacy and can be measured non-invasively and cost-efficiently thus enabling serial determinations.

Patients and methods

Blood samples were prospectively and consecutively taken prior to, 3, 6, 24, and 48 hours after SIRT from 21 breast cancer patients (median age 63.9 years, range 43 – 73 years, median time from initial diagnosis to SIRT 103.1 months (11 – 336 months)), who were suffering from diffuse hepatic metastases but with otherwise stable disease and who were treated with SIR therapy at the University Hospital Munich-Grosshadern between May 2006 and May 2008.

Inclusion criteria were good performance status (ECOG ≤ 1) and extensive liver disease excluding surgical resectability or locoregional ablation. Exclusion criteria were previous external beam radiation of the liver and recent treatment with capecitabine, significant extra hepatic tumor burden, evidence of insufficient liver function (bilirubin > 2 mg/dl, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 150 U/l, albumin < 3 mg/dl), platelet count < 50,000/µl, portal vein occlusion and significant hepatopulmonary shunting > 20% detected in pretherapeutic Tc-99m MAA scan. The study was approved by the local ethics committee and written informed consent for additional blood collection and data acquisition was obtained from each patient before radioembolization.

Selective Internal Radiation Therapy was performed as described earlier [5]. For estimation of therapy response, staging in-
Investigations were performed by PET/CT and MRI of the liver after a median of 94 days. According to RECIST criteria assessment, there was no change of disease in 5 patients, while in 16 patients, progressive disease was observed. Additionally, 1-year survival of the patients was monitored. Only 6 of the patients survived 1 year after SIRT, while 15 patients did not.

Levels of established breast cancer biomarkers CA 15-3 and CEA as well as the cell death marker cytokeratin-19 fragments (CYFRA 21-1) were measured with ElecSys (Roche Diagnostics, Mannheim, Germany). Levels of lactate dehydrogenase (LDH), C-reactive protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, gamma-glutamyl-transferase (GGT), alkaline phosphatase (AP), amylase, lipase and choline esterase (CHE) were determined by high-end analyzer AU 2700 (Olympus Diagnostics, Hamburg, Germany).

For analysis of marker changes over time the Wilcoxon test for paired samples was used, while for comparison of marker levels at the various time points with response to therapy and with one-year survival the Wilcoxon-Mann-Whitney test was used. A p-value of < 0.05 was considered statistically significant. All calculations were performed with SAS software (version 9.2, SAS Institute Inc., Cary, N.C., USA).

**Results**

As early as 24 hours after therapy, almost all parameters increased significantly, including the cell death markers cytokeratin-19 fragments (CYFRA 21-1) and LDH, the inflammatory parameter CRP, as well as the liver enzymes ALT and AST, whereas CHE, AP and amylase decreased. The most incisive dynamic was seen in CYFRA 21-1 showing a 20-fold increase 24 hours after SIRT. As expected, the slow reacting tumor markers CEA and CA 15-3 remained stable during the entire observation time.
Concerning therapy response, patients with progressive disease (n = 16) in staging investigations showed significantly higher values for CA 15-3 before therapy compared to patients with stable disease (n = 5) (medians 310.5 U/ml vs. 91.8 U/ml; p = 0.019). Similar results were also obtained 24 hours and 48 hours after therapy (Figure 1). For CYFRA 21-1 and all other markers, no significant differences between the response groups were found.

Comparable results were obtained from the evaluation of one-year-survival. While for CA 15-3, non-survivors had significantly higher value levels than survivors (medians of pretherapeutic CA 15-3 values: 346.0 vs. 70.6 U/ml; p = 0.011), the other biomarkers showed no significant differences in diverse prognostic groups. Most remarkably, eight out of 15 non-surviving patients had higher pretherapeutic CA 15-3 levels than the 6 patients who survived 1 year after SIRT, indicating a sensitivity of 53% at a specificity of 100%.

Discussion

SIRT is a fairly new promising locoregional therapy option for patients with hepatic metastases of breast cancer [3]. However, potential prognostic parameters for patients scheduled to undergo SIRT therapy are rare [4]. Until recently SIRT was only used as salvage therapy when almost all other treatment options had been exhausted [6]. However, recently a worldwide multicenter study started comparing combined SIRT with FOLFOX versus FOLFOX alone as first-line therapy in colorectal cancer patients with liver metastases too extensive for surgery [7]. Following this example, SIRT may also be included in earlier therapy concepts of other tumor entities, such as patients with liver metastases of breast cancer.

In this study, a broad panel of biomarkers relevant for various features of tumor biology and treatment effects was monitored for the purpose of pretherapeutical patient stratification and early estimation of therapy efficacy. As expected, concentrations of all examined parameters showed significant alterations already 24 hours after SIRT with the exception of the oncological markers CEA and CA 15-3, which remained stable during the entire examination period. In particular, the cell death biomarker CYFRA 21-1 increased dramatically during the first day after SIRT. Concerning therapy response estimated by PET/CT and MRI at staging investigations, only pre- and posttherapeutic CA 15-3 showed a predictive impact, while all other markers did not. Similar results were obtained regarding estimation of prognosis for one-year survival. The poor outcome of the patients may be explained by the very late stage disease in all patients included into SIRT treatment in this study. In these cases, monitoring of the therapy response after it had been applied does not appear to be highly relevant. However, it is questionable whether treatment should be applied or not at all. Therefore, pretherapeutic indicators of prognosis could provide important information for patient stratification. Interestingly, we were able to identify eight out of 15 non-surviving patients with higher pretherapeutic CA 15-3 levels than the 6 patients who survived one year after SIRT, resulting in a 53% sensitivity at a 100% specificity. At least for these patients, it could be discussed whether SIR therapy at this late stage of the disease is really helpful in improving their outcome.

In an earlier study in colorectal cancer patients with liver metastases who were treated with SIRT, we found several markers to be predictive for therapy response or prognostic for overall survival, inter alia the oncological biomarkers carcino-embryonic antigen, cancer antigen 19-9, cell death markers nucleosomes and CYFRA 21-1, C-reactive protein and several liver enzymes [5]. The fact that most of these markers were not relevant in the present setting may be explained by the low number of patients enrolled and, particularly, by the low number of patients with favorable outcome. Nevertheless, the samples investigated included a very homogenous group of patients with progressive breast cancer and extensive liver metastases. Complete sets of marker values were available for all patients at defined time points. All preanalytic steps between blood drawing, laboratory processing, and deep-frozen storage of the samples were thoroughly controlled following a strict preanalytic protocol. Biomarker measurements were performed by experienced laboratory staff independent of any clinical data collection and statistical evaluation.
Conclusion

This is the first pilot study on the predictive and prognostic relevance of pre- and post-therapeutic levels of oncological, cell death, organ-related and inflammatory biomarkers in late stage breast cancer patients with extensive liver metastases treated with Selective Internal Radiation Therapy (SIRT). CA 15-3 has been identified as a valuable marker for pretherapeutic stratification of patients and early estimation of response to SIRT.

References


