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Comparative study of YKL-40, S-100B and LDH as monitoring tools for Stage IV melanoma ☆

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ABSTRACT

Background: Serum markers can be important tools for the prognostic classification and the treatment monitoring in cancer patients. Recently, the potential new serum marker YKL-40 has been introduced for patients with malignant melanoma. The purpose of this study was to assess the prognostic value of YKL-40 in stage IV melanoma patients regarding treatment outcome and survival compared to the established markers LDH and serum S-100B and to evaluate their ability to discriminate between different stages of the disease.
Methods: YKL-40, LDH and S-100B were measured in serum samples of 50 patients with stage I/II melanoma and 61 patients with metastatic melanoma before and after treatment. Univariate and multivariate analyses were performed to determine prognostic factors.
Results: YKL-40, S-100B and LDH correlated significantly with the stage of disease. In stage IV melanoma patients, only the baseline serum levels of S-100B were significantly associated with treatment response ($p = 0.031$), but not those of LDH ($p = 0.193$) or YKL-40 ($p = 0.186$). We found a strong correlation between treatment response and unchanged or declining S-100B levels over time ($p = 0.003$, OR: 9.52, 95%-CI: 1.87–47.62), but no significant correlation between treatment response and serum changes for LDH ($p = 0.534$) and YKL-40 ($p = 0.306$), respectively. In the Cox Regression analysis, only the serum levels of S-100B proved to have a significant prognostic impact on survival ($p < 0.0001$).
Conclusion: In melanoma patients, serum levels of YKL-40, S-100B and LDH correlate significantly with the stage of disease. In stage IV melanoma, S100-B significantly correlates with treatment response and survival and is superior to LDH and YKL-40.

1. Introduction

In advanced metastatic melanoma (American Joint Committee on Cancer (AJCC) stage IV) the prognosis is still poor and the median overall survival time is 6–12 months only.[1] In addition to an improvement in the available therapeutic regimens, it is essential to identify patients who will more likely respond to systemic treatment with better long-term outcomes. Identifying prognostic factors for predicting the clinical course of the disease is, therefore, crucial.

Routine imaging methods and laboratory tests are part of the regular follow up protocol for detecting and treating metastases as early as possible. Lactate dehydrogenase (LDH) is not specific to melanoma metastases, but it has been

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shown that serum concentrations correlate with prognosis and the tumour load.[2–4] Thus, due to its prognostic impact as well as its easy, cost-efficient and widely distributed detection methodology, LDH has been implemented in the AJCC melanoma staging system in 2001.[5]

Melanoma-associated molecules are also potential candidates for serum markers. Amongst those markers, protein S-100B has been shown to correlate with clinical stage, course of the disease and survival of melanoma patients by several investigators.[6–8] Recently, two large-sized studies on high-risk melanoma patients receiving adjuvant treatment with IFNα revealed that serial determinations of S-100B serum levels are a strong independent prognostic factor for survival.[9,10] Furthermore, several authors reported that the prognostic impact of S-100B is superior to LDH serum concentration in advanced metastatic melanoma.[11–17] Thus, Swiss and German guidelines recommend determination of S-100B in serum of patients with Breslow > 1 mm lesions every 3–6 months.[18,19] However, both markers failed to be of prognostic relevance in early stage tumour-free patients.[20,21] Thus, there is further need for identifying appropriate biomarkers.

Recently, a new, promising serum marker has been introduced in malignant melanoma: YKL-40, a 40 kDA heparin binding glycoprotein, is physiologically expressed by different kinds of cells including activated macrophages and neutrophils and has been reported to act as an antiapoptotic protein by initiating the Mitogen-activated protein (MAP) kinase-pathway.[22] It has been found in peritumoural macrophages, which implies a role in tumour surrounding vascular formation and matrix degradation.[23,24] Besides this, elevated serum levels of YKL-40 were reported to be a prognostic factor for poor clinical outcome in various kinds of solid cancers.[25–28]

YKL-40 was reported as a prognostic factor for relapse-free survival and overall survival in AJCC stage I and stage II melanoma patients.[29] In patients with advanced metastatic melanoma, YKL-40 has been described to correlate with the site of metastases and poor performance status as well as with overall survival.[30] However, these reports were performed by one single centre and, to date, there are limited data of confirmatory studies addressing the prognostic value of YKL-40 for treatment monitoring purposes. Moreover, there do not exist comparative investigations with other serum markers like LDH and S-100B.

The aim of our study was to assess the prognostic impact of YKL-40 compared to the established markers LDH and serum S-100B: First, our goal was to determine a possible correlation between the serum marker levels and early and advanced stages of the disease. Furthermore, in stage IV melanoma, we evaluated their usefulness in treatment monitoring and assessed their prognostic impact regarding progression-free and overall survival.

2. Patients and methods

2.1. Patients and treatment

Basic clinical data and tumour specific data from 111 patients, who were treated with melanoma at the Department of Dermatology, University Hospital of Schleswig-Holstein, Campus Kiel, from 2007 until 2009, were analysed. Staging of the patients was performed according to the American Joint Committee on Cancer (AJCC) classification of 2002.[5] The study population consisted of two groups: Group I ($n = 61$): patients with advanced metastatic melanoma (AJCC stage IV: M1a–M1c) receiving surgical, radiotherapeutic or systemic treatment; Group II ($n = 50$): melanoma patients with primary cutaneous melanoma without metastatic disease of the lymph nodes (AJCC stage Ia–IIc: pT1a–pT4b, N0, M0). Patients with severe concomitant conditions or secondary malignancies were not included.

Patients provided written informed consent. This study was approved by the local Ethics Committee.

2.2. Tumour marker assays

Blood samples were collected in Group I prior to treatment (visit 1: start of treatment ± 7 days) and after the first treatment course (visit 2: assessment examination/end of treatment ± 7 days), in Group II after surgical resection of the primary tumour. Serum samples were investigated immediately for LDH- and S-100B-concentrations. For YKL-40 measurement, the blood samples were collected, serum was separated and frozen immediately after blood extraction. Samples were stored at −80 °C until the final analysis was done.

Total LDH activity was measured with an automated controlled system (reagent and analyser: Roche/Hitachi 747, Roche Diagnostics, Mannheim, Germany). The assay was performed according to the manufacturer's instructions. For interpretation of LDH levels in serum the upper institutional limit of 240 units per litre was chosen.

For protein S-100B measurement, we used the Elecsys® S100 assay (Roche Diagnostics, Mannheim, Germany), which forms a sandwich complex with both the biotinylated MoAb S23 and MoAb S53 conjugated with a ruthenium complex. In a second step, the complex binds to a solid phase by biotin/streptavidin interaction. We used a serum concentration of 0.11 μg/l for S-100B as the upper institutional limit (reference range) according to the manufacturer's instructions.

For measurement of YKL-40 serum levels, a commercial two-site, sandwich-type enzyme-linked immunosorbent assay (ELISA; TECOmedical GmbH, Bünde, Germany) was chosen, using a microassay plate coated with streptavidin, a biotinylated murine monoclonal antibody to human YKL-40, an alkaline phosphatase-conjugated rabbit polyclonal detection antibody to YKL-40 and a chromogenic substrate. The lower limit of detection was 10 ng/ml. We used a serum concentration of 125 ng/ml in men and 93 ng/ml in women as the upper institutional limit (reference range) according to the manufacturer's instructions.

2.3. Follow-up and further treatment

Patients with advanced metastatic melanoma (AJCC stage IV = Group I) underwent an extensive assessment programme prior to the initiation of treatment and were referred to computed tomography (CT) of the chest and abdominal tract, magnetic resonance imaging (MRI) of the brain and bone scan to exclude distant metastasis. Objective responses (OR) were re-assessed by subsequent MRI/CT scans four weeks later. If progressive disease (PD) was detected, surgical excisions