

Immunohistochemical study of the epithelial-mesenchymal transition phenotype in cancer of unknown primary: incidence, correlations and prognostic utility.

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Source

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Abstract

BACKGROUND:

The epithelial to mesenchymal transition (EMT) has been associated with metastatic dissemination and poor outcome in several solid tumour types. Our aim was to study its incidence and its prognostic significance in cancer of unknown primary (CUP).

PATIENTS AND METHODS:

One hundred tumour samples of CUP were loaded in tissue microarrays and were studied for immunohistochemical (IHC) expression of E-cadherin, N-cadherin, vimentin, the EMT transcription factor (SNAIL) and the stem cell marker octamer-binding transcription marker 4(OCT4). An EMT phenotype was defined as low expression of E-cadherin, expression of N-cadherin with/without vimentin with concomitant expression of SNAIL, as assessed by percentage of tumour cell staining.

RESULTS:

Among 100 CUP cases, the histological diagnosis was adenocarcinoma in 55, squamous carcinoma in 20 and undifferentiated carcinoma in 15, with a high grade seen in 46. Therapy consisted of palliative chemotherapy, mostly platinum based. The median progression-free survival and overall survival (OS) were 7 and 12 months respectively. Distributional studies resulted in selection of IHC cut-offs for E-cadherin (negative when expressed in <60% of tumour cells), N-cadherin, vimentin (positive when expressed in $\geq 40\%$ of tumour cells), SNAIL (positive when stained in $\geq 80\%$ of tumour cells). An EMT phenotype was observed in 8 cases (8.1%) and was strongly associated with poor OS (median OS EMT(-)=13 months vs. median OS EMT(+)=8 months, $p=0.023$). When we used staining intensity (H-Score), an EMT phenotype was observed in 16 patients and carried borderline adverse prognostic utility for outcome (median OS 9 vs. 14 months, $p=0.07$). The presence of the EMT phenotype correlated significantly with male gender, high grade and presence of visceral metastases (χ^2 $p<0.05$), while EMT mediator expression was correlated to high NOTCH 2/3 expression. Other factors, prognostic for poor survival, were male gender, PS ≥ 2 , non-platinum therapy (χ^2 $p<0.05$).

CONCLUSION:

EMT is infrequently seen in tumours of CUP. However, an adverse prognostic significance for patient outcome has been identified and may warrant studies of therapeutic targeting.