

Prognostic significance of WNT and hedgehog pathway activation markers in cancer of unknown primary.

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Abstract

BACKGROUND:

Cancer of unknown primary (CUP) possesses distinct biology and peculiar natural history, in which the roles of the winged and hedgehog signalling pathways are unclear.

MATERIALS AND METHODS:

We constructed tissue microarrays and studied the immunohistochemical (IHC) expression of β -catenin, smoothed (SMO) and the transcription factors TCF, LEF, GLI1 in 87 CUP cases for prognostic significance.

RESULTS:

A low rate of IHC expression of proteins was seen, the cut-off used being any expression in $\geq 1\%$ of tumour cells. At univariate analysis, only nuclear IHC SMO expression displayed a statistically significant association with favourable outcome [median Overall survival (OS) of 19 months in SMO-positive vs. 12 months in SMO-negative cases, $P = 0.01$]. An activated Wnt pathway, defined as IHC expression of any of nuclear β -catenin, TCF and LEF, was significantly associated with favourable progression free survival (median 9 vs. 5 months, $P = 0.037$) and OS (median 19 vs. 13 months, $P = 0.04$). This prognostic impact on OS was mainly driven by nuclear expression of TCF and/or LEF ($P = 0.03$). No prognostic significance of the hedgehog pathway activation status, defined as IHC expression of SMO or nuclear GLI1, could be established. A favourable prognostic impact of the concurrent activation of both pathways was observed. A trend for association of activated Wnt with response to chemotherapy (responders 67% among activated Wnt cases vs. 35% among nonactivated Wnt cases, $P = 0.07$) was observed in CUP adenocarcinomas.

CONCLUSIONS:

Activation of the Wnt pathway was a positive prognostic factor in a small CUP series, possibly via enhanced chemosensitivity. Independent validation is warranted.