S11. C-erbB-2 OVEREXPRESSION AND AMPLIFICATION IN UTERINE SARCOMAS

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Introduction: In the last decade, there has been a great interest in the c-erbB-2 or Her-2/neu proto-oncogene with regard to tumour biology in a large spectrum of malignancies. The C-erbB-2 proto-oncogene is located on the long arm of chromosome 17 and encodes a transmembrane tyrosine kinase growth factor that has similarities to the epidermal growth factor receptor [1]. The largest study investigating c-erbB-2 in endometrial cancer found overexpression in 15% of cases [2]. However, serous endometrial cancer showed overexpression of c-erbB-2 in 60% [3]. Given the significant c-erbB-2 overexpression in aggressive endometrial cancer, we investigated whether uterine sarcomas showed a similar pattern.

Patients and methods: All cases of uterine sarcomas that we encountered in our database from January 1990 to July 2003 were included. After central review, representative biopsies were immunohistochemically stained for c-erbB-2 (anti-HER-2/neu monoclonal antibody, DAKO). Only biopsies of carcinosarcoma with presence of both the epithelial and mesenchymal components were included. C-erbB-2 positivity was graded as follows: negative (−), weakly positive (+), moderately positive (++) and strongly positive (+++). Only membrane staining was considered positive. The carcinoma and sarcoma components of carcinosarcomas were analysed separately. Fluorescent *in situ* hybridisation (FISH) was performed on cases with c-erbB-2 overexpression.

Results: Seventy uterine sarcomas originating from 59 patients were evaluated (52 primaries and 18 recurrent). Absence of c-erbB-2 overexpression was noted in 10 adenosarcomas (9 primaries, 1 recurrence), in 21 ESS (10 primaries, 11 recurrences), and 10 leiomyosarcomas (7 primaries, 3 recurrences). Among patients with undifferentiated sarcomas, 1/4 (25%) stained 2+ and positivity was confirmed in the recurrent tumour (3+). Twenty-two primary carcinosarcomas were scored. The epithelial component was negative in 7 cases (32%), 1+ in 9 (41%), 2+ in 4 (18%), 3+ in 1 (5%) and could not be evaluated in one case, whereas the sarcoma component stained negative in 18 cases (82%), 1+ in 3 (14%) and 3+ in one (5%) case. In two recurrent carcinosarcomas, the epithelial component stained 3+ in both cases, whereas the sarcoma component scored negative and 1+.

Amplification of c-erbB-2, as determined by FISH, was observed in 5 cases with 2+ or 3+ overexpression.

Discussion: This study was the first to investigate c-erbB-2 in undifferentiated uterine sarcomas and showed immunohistochemical overexpression and amplification of the c-erbB-2 gene in 1/4 (25%) of cases. The lack of efficient treatment modalities in this highly aggressive disease might be of clinical importance. In addition, we performed the first analysis of c-erbB-2 in endometrial stromal sarcomas, although the results suggest absence of c-erbB-2 overexpression in this tumour type.

In the recurrent setting, we observed overexpression and amplification of c-erbB-2 in 2/2 carcinosarcomas and one undifferentiated sarcoma. The observation that one of these carcinosarcomas stained negative in the primary tumour, suggests a shift of regulators controlling the cell cycle during tumour evolution. The hypothesis that c-erbB-2 mainly contributes to the malignant cell cycle in the recurrent setting, needs to be confirmed in a larger number of cases, but given the need for effective treatment regimens in this setting might be of clinical relevance.

In uterine carcinosarcoma, 5/22 (22.5%) of cases showed overexpression of the c-erbB-2 gene. Given the toxicity profile of the most active agents, including cisplatin and ifosfamide, our data might suggest a role for trastuzumab in the treatment of this tumour type. Furthermore, the synergy between cisplatin and anti-c-erbB-2 antibodies observed in breast cancer [4], might also be applicable for uterine carcinosarcomas.

References

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