HER2-low expression and cell proliferation in urinary bladder carcinomas

M. Dumitru [1], M. Hortopan [2], M. Mihaila [3], C.M. Hotnog [3], L.I. Brasoveanu [3], M.E. Panait [1], M.M. Vasilescu [1]
(1) Institute of Oncology “Prof. Dr. Al. Trestioreanu" - Romania, (2) Clinical Institute Fundeni - Romania, (3) Stefan S. Nicolau Institute of Virology - Romania

Abstract Code: IUC26676-92

BACKGROUND

Human Epidermal Growth Factor Receptor 2 (HER2) is involved in pathways that regulate normal cells growth and differentiation. Spontaneous dimerization of HER2 receptors overexpressed in tumor cells or formation of HER2/EGFR heterodimers leads to a complex signaling network involved in uncontrolled cell growth and proliferation, contributing to cell invasion and metastasis.

In cancer, increased proliferative activity is also associated with aneuploidy and an accumulation of cells in the S and G2/M phases.

In recent years, HER2 status has been reclassified and tumors with lower levels of HER2 protein expression (HER2-low) are now recognized as a distinct category highly sensitive to anti-HER2 antibody-drug conjugate (ADC) therapy in breast cancer.

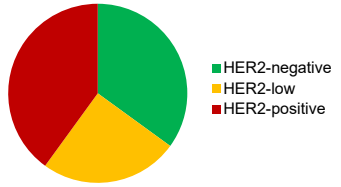
The objective of this study was to assess whether HER2-low expression is related to indicators of cell proliferation like EGFR expression and nuclear DNA content in urinary bladder carcinomas.

METHODS

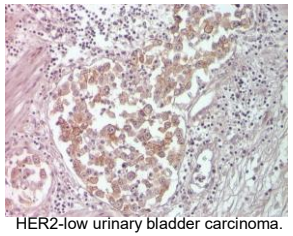
- Tumor samples were obtained from 20 patients with a mean age of 62 years (range 51 to 78).
- Formalin fixed, paraffin embedded sections of urinary bladder carcinomas (grade G1/G2, G2 and G2/G3) were investigated:
  - immunohistochemical (IHC) for HER2 and EGFR expression,
  - by in situ hybridization (ISH) for HER2 amplification.
- HER2 status was appreciated as negative (IHC 0), low (IHC 1+, IHC 2+/ISH-) and positive (IHC 3+, IHC 2+/ISH +).
- EGFR protein expression was scored as negative (IHC 0 and 1+) and positive (IHC 2+ and 3+).
- HER2 amplification was defined as more than five dots or large or small clusters or mixtures of multiple dots and clusters of HER2 gene per nucleus present in >50% of cancer cells.
- DNA content from a single cell suspension (freshly frozen tissue) was analyzed by flow cytometry for cell cycle phases and DNA ploidy level.

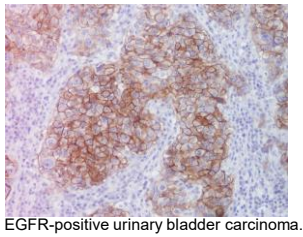
RESULTS

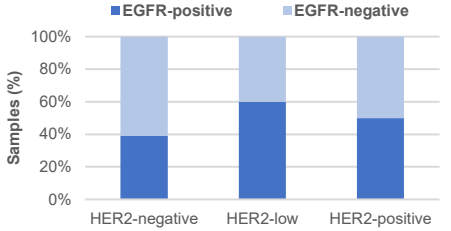
- HER2-low expression was present in 25% of urinary bladder carcinomas.



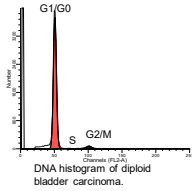
HER2 expression in bladder carcinoma


HER2-low urinary bladder carcinoma.

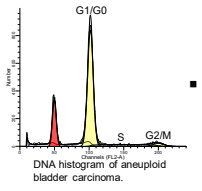

EGFR-positive urinary bladder carcinoma.



- Two of the three tumors HER2-low and EGFR positive were aneuploid and with lymph node metastases.

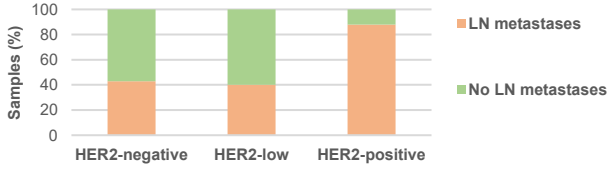


DNA histogram of diploid bladder carcinoma.

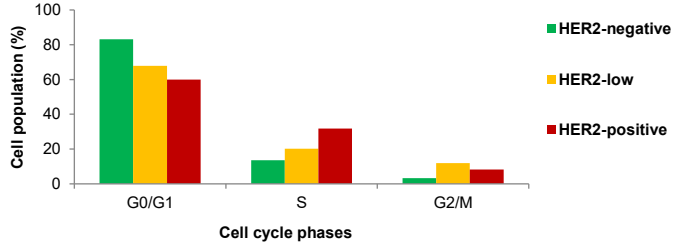


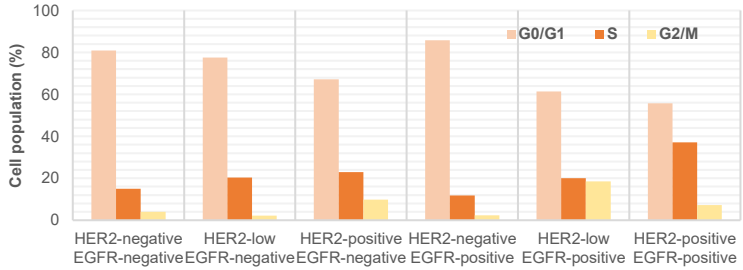
DNA histogram of aneuploid bladder carcinoma.

- No difference was observed regarding the incidence of lymph node (LN) metastases in HER2-low group and HER2-negative group.

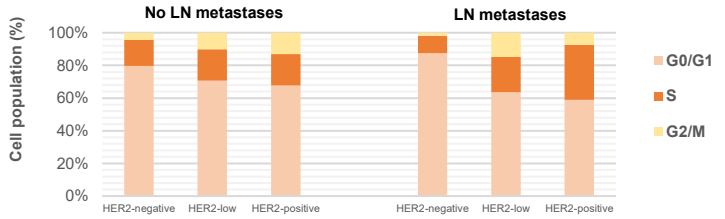


- The values of S-phase fraction and G2/M phase were higher in HER2-low tumors than in HER2-negative tumors.





- In the HER2-low tumor group, no significant differences in cell cycle phases were observed between cases with and those without lymph node metastases.



- Cell cycle phase values were higher in HER2-positive bladder carcinomas than in HER2-negative and HER2-low tumors.

CONCLUSIONS

- The HER2-low urinary bladder carcinomas seem to have a higher proliferative activity than HER2-negative tumors.
- These HER2-low cases may be new candidates for anti-HER2 ADC therapy for bladder cancer.
- This study needs to be expanded to establish the significance of HER2-low expression in bladder cancer.