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Her2 In Gastric Cancer In Albania _____

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General background

Gastric cancer (GC) is the fourth most common cancer in Albania. HER2-positivity rates in GC are reported with a wide range. There is no data for it in Albania.

Materials and method

A total of 192 patients, with primary GCs was retrospectively analyzed for HER2 overexpression by IHC. Dual SISH, was used in only 20 GCs with equivocal results. We dispersed HER2 results by: gender and age, histopathological diagnosis and stage, type of the specimen. The results were compared.

Results

We examined by IHC 73.4% (141 cases) surgical and 26.5% endoscopic biopsies: 18.4% (26 cases) and 15.7% (8 cases) HER2 3+, respectively. HER2 overexpression (3+) was detected in 17.7% (34 cases). HER2 equivocal (2+) was detected in 24.5% (47 cases). 17.8% , 14%, 4.7% were respectively intestinal type, diffuse, signet ring and the rest adenocarcinoma NOS. GC prevailed in the group age of 61-70 yrs

(31.70%;), followed by 51-60 yrs (25%), 22.9% in 71-80-yrs. 20 cases analyzed by SISH, showed Her2 amplification in 40% (8cases). Economical restrictions and problems with preanalytical phase made it impossible to evaluate by SISH all 20 cases.

Conclusion

17.7% of Albanian patients with primary GC were HER2-positive on IHC. There is no difference in biopsy and surgical specimen results. Economical restrictions can influence the results.

General background

Gastric adenocarcinoma is one of the most frequent neoplasms in the world. Its incidence varies from country to country, having higher incidences in Japan, Chiles, Finland, and a low incidence in Thailand and in most parts of Africa. In United States, the incidence of gastric cancer has decreased during the last 50 years and actually it has an incidence of 10 cases per 100 000 inhabitants.¹

In Albania, in 2008, the population was 3,170,048. According to INSTAT 45% of the population lives in the urban areas, 55% lives in the rural areas. The median survival age is 72.1 years for males and 78.6 years for females (2005-2008). Gastric cancer has a survival rate of 5 years of approximately 5-20%. Yet, there is no standard chemotherapy for patients with gastric cancer in the world.

In patients without metastasis and with tumors resectable by surgery, the main therapy (with curative purpose) is surgical excision, followed by chemotherapy or radiotherapy, according to the stage and type of tumor. The carcinomas of the antrum, body and fundus can be divided in two main histologic types: intestinal and diffuse (Lauren classification) which have different causes, different precursor lesions and different growth rates.⁴

The terminology used and the histopathologic evaluation have interobserver subjectivity mostly for two important elements of carcinogenesis, that are, atrophy and dysplasia. Microscopically, even in the early gastric cancer, also in the advanced forms, the histologic aspect is similar, with glands being from well differentiated, to moderately and poorly differentiated. There is also a subtype with cells with the aspect of "signet ring".³ There aren't yet specific molecular markers for the diagnosis of gastric cancer, even though the later is rarely a challenge for the pathologist. The amplification of HER2/Neu seems to be a marker of the ability to metastasize and a marker of poor prognosis. This can result in an effective target for the therapies with molecular base.²

Materials and method: We have conducted an epidemiologic study on the status of HER2 in gastric cancer in our country. This is a retrospective and prospective study, that consists in the collection of 192 cases (paraffin blocks) of endoscopic biopsy specimens, but also in surgical specimens of two central laboratories of Pathologic Anatomy (Laboratory of Morphologic Diagnosis and the Central Laboratory of Pathologic Anatomy, NUHC "Mother Theresa"). All the samples were examined for the expression of HER2 with immunohistochemical method and some with HER2/SICH. We have analyzed the data of the pathologic reports to check the correlation between the presence of HER2 expression and clinical-pathologic features. The immunohistochemical exam is performed with the manual method with the antibodies HercepTest™ (Dako), but also with the automatized method with BenchMark XT with the antibody anti-HER-2/neu (4B5) Rabbit Monoclonal, also SISH utilizing INFORM HER2 DNA Probe. All the data were analyzed utilizing Microsof Excel.

Results: From 192 cases examined, the demographic data show a median age of approximately 58.4 years, predominantly of the group age 6-71 yo (Table 1). In all the cases examined, 69 cases (35%) were endoscopic samples and 123 cases (65%) were surgical specimens. 9 cases (4.7%) were T4, 91 cases (47.4%) were T3, 23 cases (11.98%) were T2 and 69 cases (35%) had no tumor stage (corresponding to endoscopic biopsies). From all the cases examined with immunohistochemistry for HER2, HER2 0 was found in 53 cases, HER2 1+ in 57 cases, HER2 2+ in 47 cases and HER2 3+ in 34 cases. In 47 cases that resulted HER2 2+ (equivocal), which were impossible to be defined with immunohistochemistry for the status of amplification of HER2 gene, we have performed SISH for 20 cases, with the following results: SISH positive in 8 cases (17%) and SISH negative in 12 cases (15.5%) (table 2).

After correlating the histologic subtype with HER2 expression, it resulted that poorly differentiated adenocarcinomas (G3) had overexpression of HER2 (Her2 3+) more than well differentiated ones (G1) (respectively 23.5% vs.11.7%). Mucinous adenocarcinomas mostly have no amplification of HER2 gene, respectively 15.2% Her2 0 and 3.5% Her2 1+, and zero cases with Her2 3+. Similar data are also for the carcinoma with signet ring cells, 2.9% of which being Her2 3+ and 8.4% Her2 0.

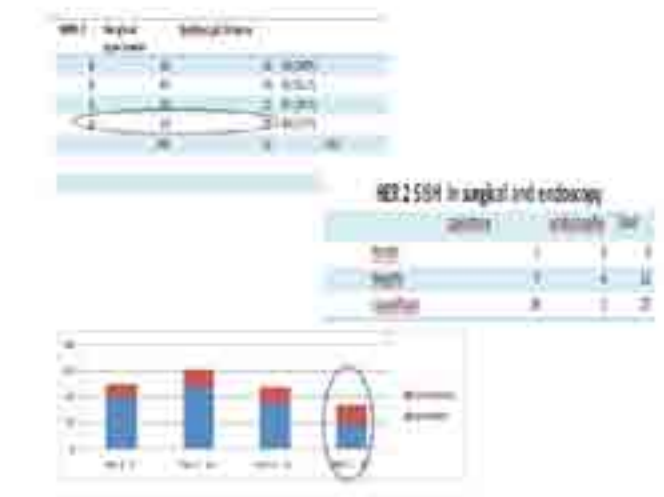
Also, even though intestinal type adenocarcinomas have a favorable prognosis in comparison to diffuse subtype, in our study, 8.8% of the cases with intestinal type cancer had amplification of HER2 gene and 20.4% of diffuse infiltrative carcinomas don't have amplification of HER2 gene (table 3).

After correlating the expression of HER2 with pathologic stage, we found no significant difference between the stage and expression of HER2 (HER2 3+) in our study (T4 2.9%, T3 35.3%, T2 8.8% and 52.5% not specified).

TABLE 1,2,3 of median age, dispersion of Her2 and correlations with the histologic type and stage.



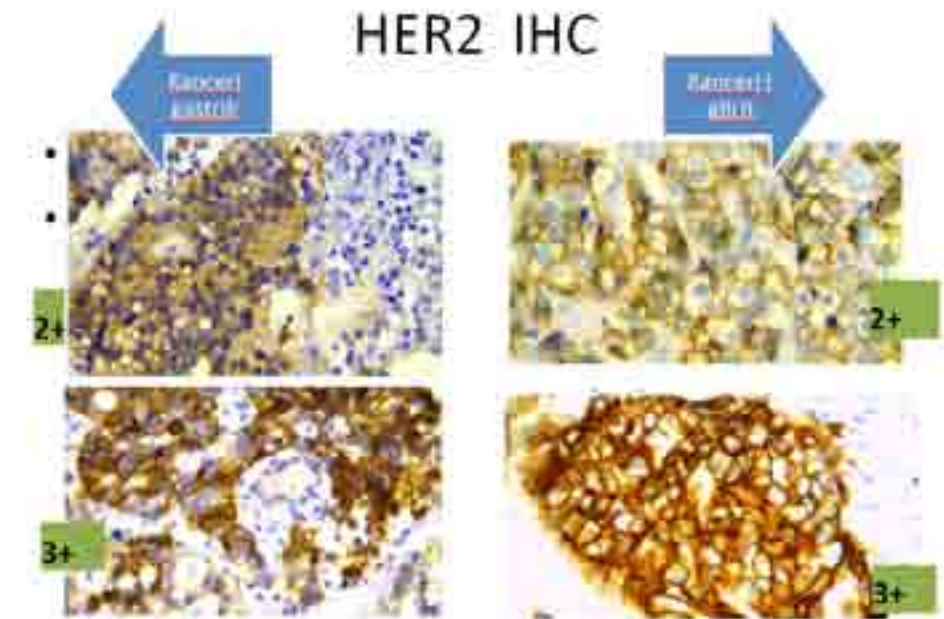
FIGURE 1 Correlation of HER2 expression in endoscopic samples and surgical specimens.



Discussion: In patients with gastric cancer and gastroesophageal cancer, the amplification of HER2 identifies the patient that will benefit from therapy with Trastuzumab. The evaluation of HER2 status is, however, influenced by the preanalytic and postanalytic parameters, as reported also for breast cancer.²

In a study of Kapelessor et.al, from 5426 tissue fragments examined with microprobes, HER2 was found mostly expressed in intestinal type and in the cancers of low grade and had no correlation with the age, gender, stage, and tumor location. Even in a study of Moelans CB and co., it was seen a low expression of HER2 in early gastric cancer. In our study the data are different, with amplification found in poorly differentiated subtypes and intestinal subtype. The abovementioned data can be explained with the biologic characteristics of gastric cancer in our country, or, another hypothesis, can be also not standardized protocol of TNM reporting system that produces variables that can influence the result. However, 17,7% of our cases express HER2 and can be a group that can benefit from targeted therapy.⁵

FIGURE 2 The difference of expression of HER2 in gastric cancer and breast cancer.



Source of paper: Prof Kadava, LDM Tutors, Alkhorin, DUN, Malacca Tawar

The evaluation of HER2 is done utilizing microscopic examination through a semiquantitative method, based in the intensity of staining of the nuclear membrane, also the stain of the entire perimeter of this membrane. There is a difference of evaluating HER2 in the materials from breast cancer and gastric cancer. This difference is reflected also in the guidelines published for this exam. ⁶

In endoscopic biopsies, which are small biopsies with crush artifacts, especially in the periphery of the tissue, with inflammatory infiltrates, HER2 score can be influenced by artifactual changes. Even in the guidelines, there is a difference of interpretation of small endoscopic biopsies and surgical specimens. In our study there is no significant difference of expression of HER2 (HER2 3+) among endoscopic biopsies and surgical specimens (respectively 15 and 19 cases, figure 2). In gastric cancer, the status of HER2, at least partially, is influenced by the variation in the methodology used, in the instruments and the experience of the technician that perform the test. ⁷

One of the main reasons of our study in both labs was exactly the quality control done utilizing the comparison of the results among the laboratories and the methods used by each. In one study of Rüschoff J et al., there is a variability between immunohistochemistry and SISH. ⁸

In one study of Mrklic et al., to evaluate HER2 in gastric cancer and its scoring system and to standardize the method, the results of IHC method were compared to SISH, not only inside the laboratory, but also among different centers that have participated in this study. ⁹

Conclusion: The examination of HER2 is performed from nearly a decade in Albania, mostly for gastric cancer. It has changed from manual to automatized method. Mostly, this exam was performed only in one laboratory that was the central laboratory of immunohistochemistry. actually, new centers are being developed. HER2 is expressed approximately in 30% of the patients with breast cancer and in 17.7% of the patients with gastric cancer. Sharing the methodology among the laboratories will improve quality assurance for HER2 testing.

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