

HER2 heterogeneity in Breast Cancer: a case report.

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Background

The human epidermal growth factor receptor 2 (HER2) is an oncogene that stimulates cancer cell growth and division associated with increased disease recurrence and poor prognosis.

According to current guidelines, HER2 status is routinely assessed by immunohistochemistry (IHC) to stratify breast cancers (BCs) in positive (score 2+ with fluorescence in situ hybridization/FISH confirmation, or score 3+), negative (score 0), and in recently so-called "HER2-low" ones (score 1+ or 2+ with negative FISH). Unfortunately, many cases show a heterogeneous expression of HER2 in which HER2-directed therapies have been ineffective.

Case presentation

In November 2021 a 39 years-old woman with multiple lesions in the right breast and lymph nodes involvement was referred to Ospedale del Mare of Naples. At diagnostic core needle biopsy (CNB), histology revealed an invasive high grade No Special Type (NST) BC HER2 3+ with reported areas of HER2 0. Since the advanced stage of the disease, histology and age, it was decided to start therapy with paclitaxel, trastuzumab and pertuzumab. However the patient underwent clinical disease progression, so another CNB was made and sent to our department: the diagnosis of NST BC with HER2 heterogeneity was confirmed, showing areas with score 2+ and with score 1+. Hence, the patient was considered eligible for therapy with Trastuzumab-Deruxtecan (T-DXd), with an appreciable clinical reduction of the tumoral masses after just one month.

Discussion

HER2 is overexpressed in ~20–25% of BCs mainly as a result of gene amplification¹. However, there are cases with intratumoral heterogeneity in which not all neoplastic cells overexpress HER2. Recently, clinical trials²⁻³ have shown favorable results for T-DXd in BCs with heterogeneous HER2 expression because of its bystander effect with death of HER2 positive cells and also of neighboring HER2-negative cells.

In this case, we identified a heterogeneity pattern of HER2 expression which allowed starting therapy with T-DXd with good clinical results.

Conclusion

HER2 IHC evaluation is an important predictive marker of therapeutic response, also for patients without evident HER2 positivity. It must be kept in mind that HER2 heterogeneity might be present in some BCs that can benefit from new therapies with a better prognosis.

1. King CR, Kraus MH, Aaronson SA. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science*. 1985;229:974-6. doi: 10.1126/science.2992089.
2. Horisawa N, Adachi Y, Takatsuka D, Nozawa K, Endo Y, Ozaki Y, Sugino K, Kataoka A, Kotani H, Yoshimura A, Hattori M, Sawaki M, Iwata H. The frequency of low HER2 expression in breast cancer and a comparison of prognosis between patients with HER2-low and HER2-negative breast cancer by HR status. *Breast Cancer*. 2022;29:234-241. doi: 10.1007/s12282-021-01303-3.
3. Mosele MF, Lusque A, Dieras V, Deluche E, Ducoulombier A, Pistilli B, Bachelot T, Viret F, Levy C, Signolle N, Tran D, Garberis I, Le-Bescond L, Dien A, Droin N, Kobayashi M, Kakegawa T, Jimenez M, Lacroix-Triki M and André F. Unraveling the mechanism of action and resistance to trastuzumab deruxtecan (T-DXd): biomarker analyses from patients from DAISY trial. *Annals of Oncology* (2022) 33: S123-S147. doi: <https://doi.org/10.1016/j.annonc.2022.03.277>