Intratumoral heterogeneity of HER2/neu expression and its consequences for the management of advanced breast cancer

HER2/neu oncogene overexpression has become a paramount prognostic and predictive marker in invasive breast carcinoma [1]. Its expression is usually highly homogeneous in malignant tissue [2]. Some cases of intratumoral heterogeneity have, however, been reported [3] (Figure 1). The impact of this heterogeneity on the natural history of breast cancer and its consequences on clinical management are unknown. We report here three clinical cases illustrating the complexity of this topic.

Case 1: A 58-year-old woman presented with node-negative, high-grade, hormone receptor (HR)-negative, invasive breast ductal carcinoma. HER2 overexpression was observed in only 30% of invasive tumor cells, with faint staining. She underwent breast-conserving surgery, radiotherapy and anthracycline-based chemotherapy. Two years later, she presented with liver metastases. Liver biopsy confirmed metastases from breast carcinoma. HER2 staining was moderately present in 95%–100% of tumor cells (Figure 2). FISH analysis showed HER2 gene amplification with eight spots per nucleus. Complete remission, as defined by RECIST criteria, was obtained with a capecitabine–trastuzumab combination.

Case 2: A 50-year-old woman presented with homolateral axillary relapse of invasive ductal breast carcinoma. The same heterogeneous pattern of HER2 expression was observed in the primary tumor and axillary lymph node (Figure 1B). The patient was included in a clinical trial with docetaxel, trastuzumab and lapatinib and achieved a complete response. After 8 months of trastuzumab–lapatinib maintenance therapy, a new axillary relapse occurred. Biopsy demonstrated no overexpression of HER2.

Case 3: A 55-year-old woman presented with node-positive, HR-positive, invasive breast ductal carcinoma treated by mastectomy, adjuvant Adriamycin–cyclophosphamide-based chemotherapy, radiation therapy and tamoxifen for 5 years. Initial HER2 status was unknown. At the age of 65, she presented with a chest wall relapse and bone metastases. Biopsy confirmed an HR-positive invasive relapse associated with

Figure 1. (A) Invasive breast carcinoma showing heterogeneous HER2 expression (upper part of the picture, 3+ and lower part, 0+) ×20 magnification. (B) Invasive breast carcinoma showing 3+ HER2 membranous expression ×40 magnification. (C) Interphase FISH carried out on the 0+ component showing two green (CEPH 17) and two red signals (HER2) (no HER2 amplification). (D) Interphase FISH carried out on the 3+ component showing clusters of red signals (HER2) (HER2 amplification).

Figure 2. HER2 overexpressing metastatic cells in a liver metastasis.
HER2 overexpression on immunohistochemistry (IHC). Treatment with docetaxel and trastuzumab allowed a major bone and local response. Surgical resection of the chest wall showed residual HR-positive invasive carcinoma, but without HER2 overexpression.

We report three clinical cases raising the issues of intratumoral heterogeneity of HER2 expression, the natural history of this particular subset of tumors and consequently their management at both early and advanced stages. HER2 status is usually not modified by therapy [4]. In a consecutive series of >600 HER2-positive breast cancers treated at Institut Curie, ~5% exhibited intratotal heterogeneity of HER2 overexpression, as shown by both IHC, according to French validated methods [5] and FISH (Figure 1). None of these three patients received trastuzumab in the adjuvant setting. These cases show that HER2 status in metastases may be similar to that of the primary tumor (i.e. heterogeneous, case 3) or different. In case 2, liver metastases exhibited FISH-confirmed HER2 gene amplification, when HER2 status was deemed heterogeneous in the primary tumor. We postulate that such cases may represent the proof that specific cell subclones may evolve separately. HER2-positive cells may account for metastatic progression. If this is the case, biopsies should be carried out on metastases from primary tumors with heterogeneous HER2 expression. Cases 1 and 3 also demonstrate that HER2 status may apparently ‘change’ during HER2-targeted therapy. The first hypothesis to explain this effect is mainly a selection of one preferential subclone in the residual tumor harboring a different HER2 status than the majority of the cells in the primary tumor. Although the intimate pharmacodynamic mechanisms of trastuzumab and lapatinib have not been fully elucidated, complete eradication of HER2-positive cells is a possible hypothesis [6]. Consequently, this provides a new rationale concerning the duration of HER2-targeted therapy, which is currently being challenged by the French PHARE clinical trial [7, 8]. This issue also raises the problem of the determination of surrogate markers of the efficacy of anti-HER2 therapy, particularly in the adjuvant setting, or after complete remission from HER2-positive metastatic disease, as the heterogeneity of HER2 status in breast carcinoma opens a challenging field of research.

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