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Original Research Article

Study of the Discordance of the HR / HER2 Status between Primary Tumor and Metastases of Breast Cancer Conducted at the Aerospace Medical Center of Rabat and Comparison with Literature Data

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Abstract

Therapeutic modalities for metastatic breast cancer have not stopped progressing in recent years, in particular hormonotherapy targeting hormonal receptors (HR), and targeted therapies targeting Human Epidermal Growth Factor Receptor-2 (HER2), which allowed to improve the overall survival of patients over expressing these receptors, however, the high risk of metastatic relapse makes the prognosis remain impaired. Among the causes of these relapses, the phenotypic instability, which would be at the origin of expression change of the HR and HER 2 on the surface of tumor cells.This discordance of phenotypic expression between the primary tumor and the metastatic relapse leads to an assessment of therapeutic modalities initially undertaken? Through this work, we will compare our study about 17 female flight crew with metastatic breast cancer, conducted at the aerospace medical center of the military hospital Mohamed 5 of Rabat, with literature data.

Keywords: Breast cancer, Metastatic relapse, Discordance, Human Epidermal Growth Factor Receptor-2 (HER2), Hormonal receptors (HR).

INTRODUCTION

Despite the contributions related to various adjuvant treatments in the initial management of localized breast cancer, approximately 20% of patients will have a metastatic relapse [1]. Markers such as Hormonal Receptors: HR (estrogen receptors (ERs), progesterone receptors (RPs)) and Human Epidermal Growth Factor Receptor-2: HER2, known on the initial tumor, are then used during therapeutic decisions in the metastatic phase. HR and HER2 status are important predictive markers in the therapeutic management of breast cancer. Literature data suggest that there is discordance of status of these receptors between primitive tumor and metastatic relapse. This tumor heterogeneity implies the question of resistance to treatment in metastatic phase [2].

METHODS

A formal approval of this study was obtained from the Ethical and Protocol Committee of the Faculty of medicine of the University Mohamed 5 of Rabat. This study was conducted in accordance with the Helsinki Declaration. We conducted a retrospective study at the Aerospace medical center of the Military Hospital Mohamed 5 in Rabat, from 15th February 2016 to 15th December 2018, with the aim of studying the discordance of RH and HER2 status between the primary tumor of breast cancer and contralateral or local metastatic recurrence, and comparison of these data with literature data.

RESULTS

A total of 17 cabin crew with metastatic breast cancer was identified; this consisted of 17 female patients and no male patients. The average age of patients was between 30 and 50 years. We studied the HR and HER2 status on the primary tumor of breast cancer, and on metastasis at the time of relapse in 17 patients. The sites of biopsies at the time of the metastatic relapse were different, namely: superficial adenopathies in 1 case, the skin in 1 case, the liver in 8 cases, the bone in 4 cases, the lung in 1 case, and the pleura in 2 cases (Figure 1).

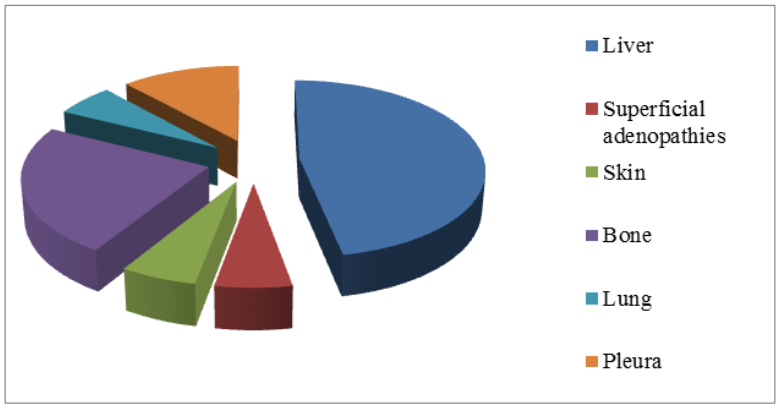

Fig-1: Different biopsy sites of the metastatic relapses

The time between the onset of the primary illness and the metastatic relapse varied between eighteen months and six years.

A change in the phenotypic status HR and / or HER2: Discordance was observed in 58% of the cases. With regard to hormonal receptors, the change in HR status from positive to negative was objectified in 17% of cases, and the change in HR status from negative to positive was objectified in 12% of cases. Regarding human epidermal growth factor receptor 2, the change of the HER2 status from positive to negative (positivity) is objectified in 6% of cases. There was in no way a change in HER2 status from positive to negative. In one case, there was a combined change in both RH and HER2 status (Table 1).

Table-1: Rates of discordance between the primitive tumor and the metastatic relapse

	Way of change	Percentage
	HR+ → HR-	17%
Hormone Receptors (HR)	HR- → HR+	12%
Human Epidermal Growth Factor Receptor-2 (HER2)	HER2- → HER2+	6%
	HER2+ → HER2-	0%

DISCUSSION

The variation of expression of HR and HER2 between the primary tumor and the metastases can modify the therapeutic decision, and thus, can in some cases improve the prognosis of the patients, that's why, a series of retrospective studies have been conducted on the variability of expression of HR and HER2 for both locoregional recurrences and metastatic relapses.

Regarding the expression of HR, few studies have addressed the issue. They were performed on a small number of patients and / or from very heterogeneous tissue materials. HR was measured by biochemical methods. Discordance rates reported varied from 10% to 40% for estrogen receptors (ER) and progesterone receptors (PR) [3], as in the case of our series: 29%. Recently, an interesting Swedish study conducted in the Karolinska Cancer Center, had interested more than 1000 patients, and had essentially focused on expression's modification of hormonal receptors (HR). The discordance rates observed for this cohort were 32.4%, 40.7% for ER, PR respectively [4].

Concerning HER2, its overexpression and/or the amplification of the corresponding gene seem to be an early event of mammary carcinogenesis, and is maintained over time, which explains the low rate of discordance found in the literature and which is close to 5% [5], near to the percentage of discordance of our series: 6%. Literature analysis reports concordance rates between primary tumor and metastases ranging from more than 80 to 100% depending on the studies and techniques used (often> 90%). A summary of published data is summarized in (Table 2).

A study of Regitnig *et al.* about 31 patients reported 15 cases of HER2 status modifications, 3 of which impacted the therapeutic decision [14]. The series of Santinelli *et al*. reported a discordance's rate of 13,3% for locoregional recurrences, and a rate of 278,6% for metachronous metastatic relapses [30]. Among the 48 patients reported by Zidan *et al*. 14% had a change in their HER2 status between primary and metastatic tumor [16].

Current data literature allows showing the phenotypic variability of tumor cells during their evolution. All these results make the case of the practice of a biopsy at the time of relapse, whether metastatic or locoregional, because it will allow an adaptation of the therapeutic decision in about 15% of cases [37].

Table-2: Results of retrospective HER2 status discordance studies

Authors	Secondary location biopsied	Number of patients (n)	Discordance rates HER 2	Rate of therapeutic modification
Masood *et al.* (6)	M [a]	50	8 %	-
Shimizu *et al.* (7)	LR [b]/M	21	0 %	-
Simon *et al.* (8)	N [c]	125	9,6 %	-
Tanner *et al.* (9)	M	46	0 %	-
Vincent-Salomon *et al.* (10)	M	44	4,5 %	-
Lindström *et al.* (4)	M	104	14,5 %	-
Gancberg *et al.* (11)	M	107	6 %	-
Taucher *et al.* (12)	LR	85	10 %	-
Burstein *et al.* (13)	LR	23	26 %	-
Regitnig *et al.* (14)	M	31	22 %	-
Carlsson *et al.* (15)	N	47	0 %	-
Zidan *et al.* (16)	M	58	14 %	7 %
Gong *et al.* (17)	LR/M	60	3 %	-
Pectasides *et al.* (18)	M	16	38 %	
Hurley *et al.* (19)	RL	23	43 %	-
D'Andrea *et al.* (20)	N	90	3,9 %	-
Harris *et al.* (21)	LR	18	11 %	-
Mittendorf *et al.* (22)	LR	25	32 %	-
Simmons *et al.* (23)	M	13	0 %	-
Lower *et al.* (24)	M	382	34 %	-
Wilking *et al.* (25)	LR/N/M	151	10 %	-
Thompson *et al.* (26)	M	137	9 %	-
Cardoso *et al.* (27)	N	370	2 %	-
Lear-Kaul *et al.* (28)	M	12	41 % IHC-0 % FISH	-
Lorincz *et al.* (29)	M	23	8,7 %	-
Santinelli *et al.* (30)	LR/N/M	119/M (35)	28,6 % M	-
Tapia *et al.* (31)	M	105	7,6 %	-
Niikura *et al.* (32)	M	182	24 %	-
Aitken *et al.* (33)	N	194	8,9 %	-
Amir *et al.* (34)	LR/M	271	10 %	14 %
Broom *et al.* (35)	M	100	5,5 %	-
Xiao *et al.* (36)	M	66	15,1 %	-

M: Metastatic relapse, LR: Locoregional relapse, N: Ganglionic relapse

Two main reviews can be made to all of these studies, first, the low number of patients included in the studies, like our studie (17), secondly, the limitations of pathology techniques used to assess the status of target receptors, for example: Immunohistochemistry (IHC) techniques are operator-dependent and have relatively limited reproducibility, the HER status assessment by FISH(fluorescence in situ hybridization) is commonly accepted as more reliable, but only a portion of these studies had used it [23,31].

CONCLUSION

The frank demonstration by the different studies that there is a phenotypic variation of the RH and HER2 status make the case for the need of a reevaluation of the tumor phenotype by performing biopsies on the metastatic sites, which would have an impact on the therapeutic decision and could improve patient survival.

Competing interests

The authors declare that they have no competing interests.

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