CHAPTER 10.

Endocrine therapy and HER2-targeted therapy for breast cancer

Key observations

- A high proportion of patients with breast cancer in Morocco can be classified by molecular subtype because hormone receptor and HER2 expression status are known. This allows tailored management.
- At CM-VI, 54.0% of patients with hormone-sensitive breast cancers received either tamoxifen or aromatase inhibitors. At INO, the proportion was 83.8%.
- The proportion of patients receiving hormone therapy is probably underreported, especially at CM-VI. Patients are prescribed the drug from the outpatients department and the information is not always entered in the case records.
- Tamoxifen was prescribed more commonly than aromatase inhibitors at both oncology centres. The use of aromatase inhibitors for postmenopausal women gradually increased over time.
- HER2 was positive in about 30% of the patients tested for the receptor at CM-VI or at INO. Trastuzumab was administered to 28.0% at CM-VI and to 45.9% at INO. The proportions are high compared with what has been reported from oncology centres in most other LMICs.
- Of the patients with HER2-positive cancer, 91.0% at CM-VI and 97.8% at INO received combination chemotherapy, most of which is taxane-based.

10.1 Principles of endocrine therapy for breast cancer

Determination of the molecular subtype of breast cancer on the basis of the ER, PR, and HER2 expression, and, preferably, Ki-67 status and tailoring treatment according to this information has dramatically changed the management of breast cancer.

All patients with ER- and/or PR-positive cancer should receive selective ER-blocking agents, such as tamoxifen, or aromatase inhibitors (anastrozole, letrozole, or exemestane), depending on menopausal status.

Adjuvant tamoxifen in patients with ER-positive disease is reported to reduce the annual odds of recurrence by 39% and the annual odds of deaths by 31%, irrespective of age, lymph node status, and use of adjuvant chemotherapy (EBCTCG et al., 2005). Although tamoxifen is effective in premenopausal women, an aromatase inhibitor is the drug of choice in postmenopausal women (Gradishar et al., 2020). The treatment should be continued for 5–10 years to get the maximum benefit.

10.2 Patients receiving endocrine therapy at CM-VI and INO

We observed that 73.4% (466/635) of patients with breast cancer registered at CM-VI and 77.6% (792/1020) of those registered at INO and for whom information on ER and PR status was available had tumours that were positive for ER and/or PR. Endocrine therapy was prescribed to 53.9% of the patients with ER- and/or PR-positive cancer registered at CM-VI and 83.8% of the patients with ER- and/or PR-positive cancer registered at INO.

10.2.1 Type of endocrine therapy prescribed

Tamoxifen was prescribed more commonly than aromatase inhibitors at both oncology centres. At CM-VI, 85.3% of the patients with ER- and/or PR-positive cancer who received anti-estrogen drugs were prescribed tamoxifen and 14.7% received aromatase inhibitors. The proportion of patients who received aromatase inhibitors was higher in 2013–2017 (18.2%) than in 2008–2012 (11.5%).

Tamoxifen was prescribed to 83.0% of the patients with ER- and/or PR-positive disease who received endocrine therapy at INO; the rest were prescribed aromatase inhibitors. The proportion of patients who received aromatase inhibitors was substantially higher in 2013–2017 (24.2%) than in 2008–2012 (7.1%).

10.2.2 Endocrine therapy by ER and PR status

The numbers of patients who received tamoxifen or aromatase inhibitors according to ER and PR status are shown in Table 10.1. Most patients at CM-VI (86.2%) had cancers that were positive for both ER and PR, and 55.9% of them received endocrine therapy; 39.1% of the patients with ER-positive and PR-negative disease and 50.0% of the patients with ER-negative and PR-positive disease received endocrine therapy.

At INO, most (84.9%) of the patients had cancers that were positive for both ER and PR, and 84.8% of them received endocrine therapy; 79.2% of the patients with ER-positive and PR-negative disease and 73.9% of those with ER-negative and PR-positive disease received endocrine therapy.

10.3 Principles of HER2-targeted therapy

The HER2-*neu* oncogene is overexpressed in 15–25% of breast cancers and is associated with increased risk of recurrence, poor response to chemotherapy, and lower survival, irrespective of hormone receptor status (Pondé et al., 2019). Trastuzumab is a humanized monoclonal antibody targeted against HER2. A single year of treatment with trastuzumab after completion of chemotherapy in non-metastatic breast cancers may reduce risk of recurrence and/or death by approximately 50%, with a significant 8.4% absolute increase in DFS at 2 years (Piccart-Gebhart et al., 2005). Similar benefits were observed in patients with metastatic breast cancer (Vogel et al., 2002).

Table 10.1. ER and PR status in patients with cancer positive for ER and/or PR who received tamoxifen or aromatase inhibitors

ER and PR combination	CM-VI						INO					
	Period of diagnosis				Total		Period of diagnosis				Total	
	2008–2012		2013–2017				2008–2012		2013–2017			
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Patients with known ER and PR status	197		268		465		334		457		791	
Received tamoxifen or aromatase inhibitors	130	(66.0)	121	(45.1)	251	(54.0)	280	(83.8)	383	(83.8)	663	(83.8)
ER+ and PR−	24		22		46		37		59		96	
Received tamoxifen or aromatase inhibitors	13	(54.2)	5	(22.7)	18	(39.1)	26	(70.3)	50	(84.7)	76	(79.2)
ER− and PR+	13		5		18		19		4		23	
Received tamoxifen or aromatase inhibitors	8	(61.5)	1	(20.0)	9	(50.0)	13	(68.4)	4	(100.0)	17	(73.9)
Both ER+ and PR+	160		241		401		278		394		672	
Received tamoxifen or aromatase inhibitors	109	(68.1)	115	(47.7)	224	(55.9)	241	(86.7)	329	(83.5)	570	(84.8)

CM-VI, Centre Mohammed VI pour le traitement des cancers; ER, estrogen receptor; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah; PR, progesterone receptor.

10.3.1 HER2-targeted therapy at CM-VI and INO

At CM-VI, HER2 was positive in 30% of the 643 patients tested for the receptor. Trastuzumab was administered to 28.0% of the patients with positive HER2 status.

At INO, HER2 was positive in 29.4% of the 1030 patients in whom HER2 status was known. Trastuzumab was administered to 45.9% of the patients with positive HER2 status.

Almost all of the patients with HER2-positive cancers who received trastuzumab were also treated with chemotherapy, both at CM-VI (91.0%) and at INO (97.8%). Most of the patients treated with trastuzumab and chemotherapy received taxane-based chemotherapy, both at CM-VI (67.3%) and at INO (88.2%).

10.4 Endocrine and HER2-targeted therapy for breast cancer in Morocco compared with other settings

10.4.1 Endocrine therapy

The EUSOMA benchmark for quality indicators in breast cancer care stipulates that at least 85% of patients with endocrine-sensitive invasive cancer should receive endocrine therapy. This benchmark was nearly achieved at INO. The proportion of patients with hormone-sensitive cancers who received endocrine therapy is lower at CM-VI, most likely because of underreporting; the drugs were often prescribed to patients without being documented in the case records.

The reported frequency of tamoxifen use for patients with breast cancer varies widely in LMICs. Studies have reported frequencies of 37.7% in Nigeria, 48.1% in South Africa, 60% in Uganda, and 92.9% in Cameroon (Sutter et al., 2016). This variation may be because some of the countries do not have immunohistochemistry facilities and all patients with breast cancer are blindly prescribed tamoxifen, or because poor-quality immunohistochemistry facilities fail to detect the receptors and report a high frequency of triple-negative disease (Kantelhardt et al., 2015; Silverstein et al., 2016).

10.4.2 Trastuzumab as anti-HER2 therapy

The EUSOMA quality indicator for breast cancer care stipulates that at least 85% of patients with HER2-positive cancers (except those with diameter < 1 cm and node-negative) should receive trastuzumab and be treated with chemotherapy. Approximately one third of the patients with HER2-positive cancer at CM-VI and half of those with HER2-positive cancer at INO were treated with trastuzumab. The drug has been included in the list of essential drugs in Morocco; this allows the public oncology hospitals to procure the drug despite its high cost.

Use of trastuzumab therapy is very limited in most LMICs both because of the lack of facilities to identify biomarkers and because of the high cost of treatment. The drug should be given for at least 1 year, and the annual cost may exceed US$ 50 000. In a survey of oncologists in the USA and some of the emerging economies (Brazil, Turkey, Mexico, and the Russian Federation), 37–49% of respondents reported prescribing trastuzumab infrequently. They cited lack of insurance coverage and/or unavailability of the drug as common barriers (Lammers et al., 2014). Trastuzumab is included in the WHO essential drug list, and biosimilars available at a price 65% lower than the cost of the originator drug were prequalified by WHO in 2015 (Davio, 2019).

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