CHAPTER 8.

Chemotherapy

Key observations

- A high proportion of the patients with breast cancer included in this study (68.0% of those registered at CM-VI and 84.5% at INO) had chemotherapy in their treatment protocol. The proportion decreased over time in both centres, possibly because of appropriate risk stratification based on the molecular and histopathological characteristics of the tumours.
- About 10–20% of the patients were treated with neoadjuvant chemotherapy. The proportion receiving neoadjuvant chemotherapy is still lower than expected, most likely because a large number of patients underwent initial surgery in settings other than the oncology centres.
- The combination of drugs, either AC60/600 (four cycles of doxorubicin [60 mg/m^2] and cyclophosphamide [600 mg/m^2] every 3 weeks) or FEC100 (5-FU [600 mg/m^2], epirubicin [100 mg/m^2], and cyclophosphamide [600 mg/m^2]) regimens along with taxane) used for both adjuvant and neoadjuvant chemotherapy is as per the international standards and the recently published guidelines for chemotherapy.
- Overall, 52.9% of the patients at CM-VI and 67.9% of those at INO who received chemotherapy were treated with a taxane, in combination with either AC60/600 or FEC100.
- The median number of chemotherapy cycles (6–8 cycles for different stages) received by the patients and the median duration of adjuvant chemotherapy (ranging from 18 to 20 weeks) indicate high compliance with chemotherapy.

8.1 Principles of chemotherapy for treatment of breast cancer

The decision to administer adjuvant chemotherapy after surgery is based on hormone receptor and HER2 expression status and pathological characteristics (size and grade of tumour, number of axillary lymph nodes involved, presence of angiolymphatic invasion, etc.). Age and associated comorbidities are also important considerations. Although chemotherapy is indicated for all HER2-positive and triple-negative cancers, the decision to administer adjuvant chemotherapy to the hormone receptor-positive and HER2-negative cases depends on the presence or absence of other risk factors.

Preoperative chemotherapy (also known as neoadjuvant chemotherapy) is increasingly recommended and practised in the management of both operable and inoperable breast cancers. No difference in long-term clinical outcomes was observed in RCTs when chemotherapy was given

before or after surgery, although neoadjuvant chemotherapy improved the chance of patients being eligible for BCS (Mauri et al., 2005).

A combination of anthracycline (doxorubicin or epirubicin) and cyclophosphamide followed by a taxane (usually paclitaxel) is the most commonly used chemotherapy regimen for breast cancer (Moo et al., 2018). Anthracycline and cyclophosphamide became the standard of care after a systematic review by the EBCTCG, which demonstrated that compared with the CMF regimen used earlier, the new regimen significantly reduced annual odds of recurrence by 12% and annual odds of death by 11% (EBCTCG, 1998). Adding sequential taxane can significantly increase the pathological response rate and overall survival and is considered to be the standard of care even for early-stage breast cancer (Cuppone et al., 2008; Fujii et al., 2015).

8.2 Details of patients receiving chemotherapy in the study

Chemotherapy practice in Morocco is guided by the national guidelines for treatment with chemotherapy (Association Marocaine de Formation et de Recherche en oncologie médicale, 2019).

In the patients registered at CM-VI, chemotherapy was administered to 68.0% of those who received any cancer-directed treatment. The proportion who received chemotherapy was higher in 2008–2012 (88.7%) than in 2013–2017 (60.7%). Of the patients who received chemotherapy, 86.2% received it as an adjuvant treatment, 10.6% received neoadjuvant chemotherapy, and just 3.2% received palliative chemotherapy. The proportion who received neoadjuvant chemotherapy remained constant over time.

In the patients registered at INO, chemotherapy was administered to 84.5% of those who received any cancer-directed treatment. The proportion who received chemotherapy was higher in 2008–2012 (94.0%) than in 2013–2017 (77.8%). Of the patients who received chemotherapy, 71.8% received it as an adjuvant treatment, 19.0% received neoadjuvant chemotherapy, and 9.2% received palliative chemotherapy. There was no major change in the distribution over time.

8.2.1 Distribution of patients receiving chemotherapy according to stage

More than three quarters (76%) of the 622 CM-VI patients who received chemotherapy had stage II or III disease. Adjuvant chemotherapy after surgery was administered to all the patients with stage I disease, 95.7% with stage II, 79.3% with stage III, and 54.5% with stage IV (Table 8.1). Most patients who received neoadjuvant chemotherapy had either stage III (19.7% received neoadjuvant chemotherapy) or stage IV disease (16.4% received neoadjuvant chemotherapy).

At INO, 7.3% of the 1018 patients who received chemotherapy had stage I disease, 41.3% had stage II, 37.1% had stage III, and 11.5% had stage IV. Adjuvant chemotherapy after surgery was administered to 87.8% of patients with stage I disease, 85.5% with stage II, 73.3% with stage III, and 12.8% with stage IV (Table 8.1). A higher proportion of patients than at CM-VI received neoadjuvant chemotherapy at INO at each stage: 10.8% of patients with stage I disease, 14.0% with stage II, 24.9% with stage III, and 18.8% with stage IV were treated with neoadjuvant chemotherapy.

Only a small proportion of patients who underwent BCS (2.2% at CM-VI and 11.1% at INO) received neoadjuvant chemotherapy. All the rest received chemotherapy as adjuvant therapy after surgery.

8.2.2 Molecular subtypes of cancers for patients receiving chemotherapy

The proportion of patients with different molecular subtypes of breast cancer who received adjuvant chemotherapy at CM-VI ranged from 88.9% for luminal-like to 97.9% for ER- and PR-negative and HER2-positive types (Table 8.1). Neoadjuvant chemotherapy was administered to 10.3% of patients with luminal-like cancer, 10.3% of patients with ER- and PR-positive and HER2-positive cancer, and 7.9% of patients with triple-negative cancers. No neoadjuvant chemotherapy was given to patients with ER- and PR-negative and HER2-positive cancers.

The proportion of patients who received adjuvant chemotherapy at INO ranged from 67.9% of patients with ER- and PR-negative and HER2-positive cancer to 74.5% of patients with luminal-like cancer. Higher proportions of patients with the different molecular subtypes received neoadjuvant chemotherapy at INO than at CM-VI (luminal-like, 17.2%; ER- and/or PR-positive and HER2-positive, 17.9%; ER- and PR-negative and HER2-positive, 21.4%; and triple-negative, 20.3%).

8.2.3 Chemotherapy regimens used

The most commonly prescribed chemotherapy regimens (adjuvant or neoadjuvant) for the patients registered at CM-VI were either AC60/600 (four cycles of 60 mg/m^2 doxorubicin and 600 mg/m^2 cyclophosphamide every 3 weeks) followed by taxane every 3 weeks or AC60/600

Table 8.1. Type of chemotherapy administered at the oncology centres by stage and molecular profile

	Patients assessed	Chemotherapy type					
	n	Adjuvant *n* (%)		Neoadjuvant *n* (%)		Palliative *n* (%)	
CM-VI							
No. of patients receiving chemotherapy	622	536	(86.2)	66	(10.6)	20	(3.2)
Stage							
I	57	57	(100.0)	0	(0.0)	0	(0.0)
II	276	264	(95.7)	11	(4.0)	1	(0.4)
III	198	157	(79.3)	39	(19.7)	2	(1.0)
IV	55	30	(54.5)	9	(16.4)	16	(29.1)
ER, PR, and HER2 status							
ER+ and/or PR+ and HER2−	243	216	(88.9)	25	(10.3)	2	(0.8)
ER+ and/or PR+ and HER2+	107	94	(87.9)	11	(10.3)	2	(1.9)
ER− and PR− and HER2+	47	46	(97.9)	0	(0.0)	1	(2.1)
Triple-negative	101	91	(90.1)	8	(7.9)	2	(2.0)
INO							
No. of patients receiving chemotherapy	1018	731	(71.8)	193	(19.0)	94	(9.2)
Stage							
I	74	65	(87.8)	8	(10.8)	1	(1.4)
II	421	360	(85.5)	59	(14.0)	2	(0.5)
III	378	277	(73.3)	94	(24.9)	7	(1.9)
IV	117	15	(12.8)	22	(18.8)	80	(68.4)
ER, PR, and HER2 status							
ER+ and/or PR+ and HER2−	501	373	(74.5)	86	(17.2)	42	(8.4)
ER+ and/or PR+ and HER2+	195	143	(73.3)	35	(17.9)	17	(8.7)
ER− and PR− and HER2+	84	57	(67.9)	18	(21.4)	9	(10.7)
Triple-negative	128	94	(73.4)	26	(20.3)	8	(6.3)

CM-VI, Centre Mohammed VI pour le traitement des cancers; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah; PR, progesterone receptor.

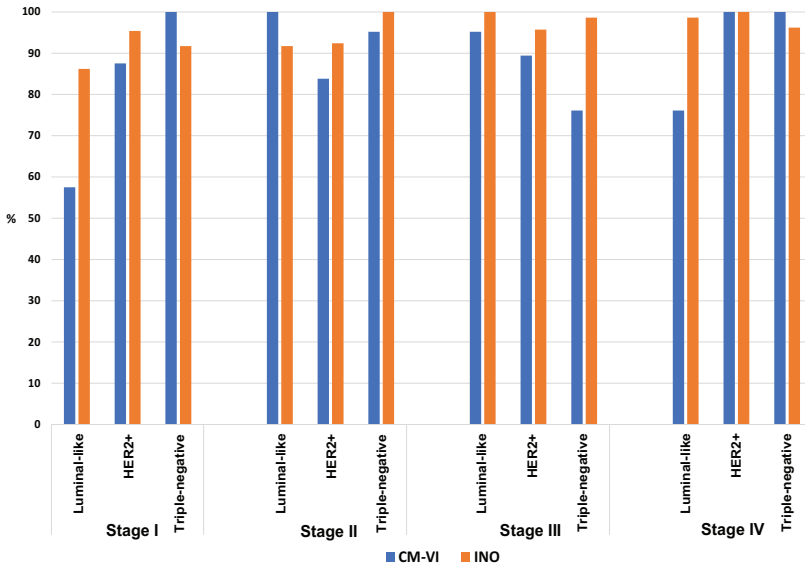
alone. Paclitaxel (80 mg/m^2) was the most commonly used taxane. The FEC100 regimen (a combination of 600 mg/m^2 5-FU, 100 mg/m^2 epirubicin, and 600 mg/m^2 cyclophosphamide) was also frequently used with or without taxane. Overall, 52.9% (320/605) of patients at CM-VI who recieved chemotherapy and 67.9% (682/1004) of patients at INO who received chemotherapy were treated with a taxane, mostly in combination with either AC60/600 or FEC100 regimens.

8.2.4 Median number of cycles of chemotherapy and duration of chemotherapy

On average, six cycles of chemotherapy were given over a period of 20–25 weeks. We estimated the

median number of cycles of chemotherapy received by the patients and the median duration over which chemotherapy was administered at the two centres. The median number of cycles of adjuvant and neoadjuvant chemotherapy for all stages and at both centres was between six and eight cycles. The median duration of adjuvant chemotherapy was between 19.0 and 20.4 weeks at CM-VI and between 18.6 and 20.0 weeks at INO. The median duration of neoadjuvant chemotherapy was between 23.7 and 26.2 weeks at CM-VI and between 22.7 and 26.6 weeks at INO. This is indirect evidence that most patients completed their chemotherapy treatment.

Fig. 8.1. Proportion of patients treated with chemotherapy (with surgery and/or radiotherapy or alone) by stage and molecular subtype. CM-VI, Centre Mohammed VI pour le traitement des cancers; HER2, human epidermal growth factor receptor 2; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.



8.3 Chemotherapy for breast cancer in Morocco compared with other settings

The oncology centres in Morocco have adopted improvements in chemotherapy as they have been developed over time. The financial protection offered by various insurance schemes has improved access to the chemotherapeutic agents for patients attending the public oncology centres. Chemotherapy was tailored to the specific biological nature of the cancer in each case. We observed that a high proportion of patients were treated with combination chemotherapy, especially if they had cancers that were HER2-positive or triple-negative, at both oncology centres (Fig. 8.1). This is in line with international recommendations. The chemotherapy regimens (AC60/600 or FEC100) used to treat breast cancers in Morocco are as recommended in the NCCN and other international guidelines, and more than half of the patients had a taxane included in the combination of drugs.

However, the proportion of patients receiving neoadjuvant chemotherapy was lower than that expected in a setting where a high proportion of cases are detected at an advanced stage. This was mainly because many patients (especially at CM-VI) attended the oncology centres after undergoing surgery elsewhere. An insignificant number of patients treated in hospitals or clinics other than the oncology centres received neoadjuvant chemotherapy.

Very little information is available on the standard-of-care management of breast cancer using chemotherapy in the Eastern Mediterranean Region or Africa. A study of 834 randomly selected patients with breast cancer diagnosed between 2009 and 2015 in 10 sub-Saharan African countries reported that of 747 patients without any known metastasis, 40.6% underwent surgery, 33.6% received chemotherapy, and 15.5% received radiotherapy. Half of the 299 patients treated with chemotherapy received an anthracycline-based regimen, and less than one third received an anthracycline regimen plus taxane (Joko-Fru et al., 2018). Many countries do not have supplies of the bare minimum number of anticancer drugs included in the WHO drug list (Ruff et al., 2016). Patients cannot afford to purchase the drugs and often do not comply with treatment (Vanderpuye et al., 2017).

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