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Management and treatment of triple-negative breast cancer patients from the NEMESI study: An Italian experience

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ABSTRACT

Aims: Triple-negative breast cancers (TNBCs) lack expression of oestrogen, progesterone, and Human Epidermal Growth Factor 2 receptors. The NEMESI study described current Italian treatment practices in patients with operable, early-stage breast cancer (EBC).

Patients and methods: Retrospective, observational study involving 63 Italian oncology centres. Eligible patients were aged ⩾18 years with EBC (stage I–II) who had undergone surgery, received ⩾1 cycle of adjuvant chemotherapy and/or adjuvant hormonal therapy and attended an oncology centre between 1 January 2008 and 30 June 2008. This subanalysis focused on patients with TNBC. Variables evaluated included: demographic data/clinical characteristics; tumour characteristics; adjuvant therapy; compliance to chemotherapy. Continuous variables were summarised using descriptive statistics.

Results: Of 1894 patients in the NEMESI study, 185 patients (9.8%) had TNBC. At diagnosis, 98 patients were aged 50–70 years and 114 were post-menopausal. Tumours were subcategorised as pT1mic/pT1a/pT1b/pT1c in 108 patients and pT2/pT3/pT4b in 77 patients. Mean tumour size was 2.1 cm, tumours were highly undifferentiated in 144 patients and 128 patients were pNO. 179 patients received adjuvant chemotherapy; anthracyclines with or without taxanes were commonly used. 145 patients received radiotherapy.

Conclusions: Adherence of Italian clinical practice to International Guidelines in the management of early-stage TNBC is satisfactory.

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1. Introduction

Breast cancer comprises a heterogeneous group of diseases that vary in terms of morphology and biology, with different tumour subtypes based on the expression of certain receptors on the surface of tumour cells.[1] Prognosis and treatment success are influenced by numerous factors, including: cancer size, stage, node positive, histological type, histological grade, patient's age and biological markers. Triple-negative breast cancer (TNBC) is in itself a heterogeneous group of diseases, which are characterised by substantial variability in morphological and pathological features.[2] TNBC, defined by a lack of expression of the estrogen receptor (ER), progesterone receptor (PgR), and Human Epidermal Growth Factor Receptor 2 (HER2), constitute approximately 10–24% of all breast cancers.[3–5] It is estimated that, world-wide, over 170,000 of the 1 million cases of breast cancer diagnosed annually will be the triple-negative subtype.[6] TNBC is diagnosed more frequently in younger women, with BRCA1 mutations and in premenopausal African and African-American women.[4,6]

Despite its relatively small proportion amongst all breast cancers, the TNBC subtype is clinically characterised as an aggressive cancer which is associated with poor outcome. Patients with TNBC relapse earlier (with higher recurrence rates during the first 1–3 years following treatment) and have higher rates of recurrence in visceral organs (lung, liver and central nervous system), with lower rates of bone disease, compared with other subtypes.[7]

Clinicopathological features include larger mean tumour size, higher grade, high proliferation rate, high nuclear pleomorphism, a pushing border of invasion and higher incidence of node positivity.[2,4] Histologically, TNBC are generally ductal invasive carcinomas, but other histologies can also be found, such as metaplastic and medullary.[8] Most TNBC are positive for cytokeratins (CK) 5/6, CK 14 and CK 17 and express markers of a high proliferation index.[1]

The majority of TNBC possess a basal phenotype and show the basal expression of various markers; however, it is important to clarify that the terms 'triple-negative' and 'basal-like' are not completely synonymous. The term triple-negative refers to the immunohistochemical (IHC) classification of breast cancer lacking ER, PgR and HER 2 expression, whereas the basal-like subtype is defined via gene expression microarray analysis; however, the triple-negative phenotype is currently considered a surrogate of the basal-like phenotype.[1,9]

The aim of the retrospective NEMESI study was to analyse data related to the adjuvant systemic treatment of patients with early-stage operable breast cancer, in order to improve knowledge of the therapeutic management of breast cancer in Italy. Preliminary data from the NEMESI study, which included 1894 evaluable patients with early-stage breast cancer, were presented at the American Society of Clinical Oncology 2010 annual meeting.[10–12] The current study will focus on the subgroup of patients from the NEMESI study with triple-negative disease.

2. Patients and methods

This retrospective, observational study was conducted at 63 academic and non-academic oncology centres (Istituto di Ricovero e Cura a Carattere Scientifico [IRCCS], and public and private hospitals and University hospitals) located in Northern, Central and Southern Italy. The centres were representative, in terms of both geographic distribution and type of institution, of the Italian situation as described in the census reported in the 2006 White Book of the Italian Association of Medical Oncology (AIOM).

Patients were eligible for the study if they met the following criteria: women aged $\geqslant$18 years; histological diagnosis of early-stage breast cancer (stage I–II according to TNM [tumour, node, metastasis] American Joint Committee on Cancer [AJCC] version VI)[13]; had undergone surgery; received at least one cycle of adjuvant chemotherapy and/or adjuvant hormonal therapy; availability of the following local staging and biological parameters: pT, pN, grade (G), ER, PgR, Ki67 or MIB-1, HER2.

Candidates for adjuvant therapy with trastuzumab and/or radiotherapy on residual breast or thoracic wall and/or regional supraclavear and/or internal breast lymph node stations were also eligible. Patients were excluded if they had received neo-adjuvant chemotherapy and/or hormonal therapy, had locally advanced and/or metastatic (stage III–IV) breast cancer or, had ductal or lobular carcinoma in situ. Data were retrospectively retrieved by each site from the patients' clinical records.

This subanalysis focused on patients with TNBC. In line with other studies[14] TNBC was defined as ER and PgR cell staining of either <1% or <10% by IHC (with a range from 0 to 9%) depending on investigational centre, and HER2 staining of <3+ by IHC or 2+ staining with no gene amplification by fluorescence in situ hybridisation (FISH).

The protocol was reviewed by the independent ethics committee of the coordinating centre. Notification of the study was also sent to the ethics committees of each participating centre, as required by Italian regulations governing observational studies (AIFA document of 20/3/2008). The protocol complied with the recommendations of the Declaration of Helsinki.

2.1. *Sample size determination and data collection*

The NEMESI study aimed to collect data from the clinical records of $\geqslant$1300 and $\leqslant$1500 patients attending at least 50 oncology centres. These figures correspond to 3.6% and 4.2%, respectively, of new cases of early-stage breast cancer recorded each year (approximately 40,000 cases, 90% of which are early stage), and 12.5% of the Italian oncology sites (approximately 400 throughout Italy).

During December 2009, each centre was requested to collect data from 10 to 30 consecutive patients with early-stage breast cancer who attended their centre between 1 January 2008 and 30 June 2008. The start of data collection was at the investigator's discretion and was not declared. Also, to minimise centre bias the percentage of patients enrolled in each study centre could not exceed 50% of the patients attending the centre during that time, and each centre had to collect the data of at least 33% of patients seen during that period. The data, collected on an electronic clinical report form, were submitted to automatic checks to assess completeness, correctness and internal coherence. Possible

discrepancies or otherwise unreliable data were submitted to the investigator in the form of queries for clarification and/or resolution.

2.2. Variables evaluated

The following variables were evaluated: demographic data and clinical characteristics (mean age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, menopause status, presence of previous breast cancer and concomitant disease); tumour characteristics (type of surgery, TNM AJCC version VI classification and staging, biological tumour characterisation [ER and PgR status, HER2 status and Ki67 proliferative index]); adjuvant therapy received (chemotherapy, radiotherapy, programmed hormonal therapy, trastuzumab, concurrent treatment with other experimental drugs in breast cancer adjuvant treatment); and compliance with chemotherapy (dosage and number of programmed cycles, dosage and number of cycles administered, dose reduction, total number of chemotherapy delays [days], reasons for dose reduction/delay of chemotherapy, possible definitive interruption of the treatment and related causes).

2.3. Statistical analysis

Statistical analysis was completed for all enrolled patients who met the inclusion criteria. For the subgroup of patients with TNBC, continuous variables were summarised using descriptive statistics, including: number of subjects, mean, standard deviation (SD), median, minimum, 25th percentile, 75th percentile and maximum. For categorical variables, summaries included counts of subjects and percentages.

3. Results

The evaluable population in the NEMESI study was comprised of 1894 patients with early-stage breast cancer who had received surgery followed by at least one cycle of adjuvant chemotherapy and/or hormonal therapy. Of these, 185 patients (9.8%) had TNBC; 172 patients had ER and PgR staining of 0%, 13 patients had ER and PgR staining between 1% and 9%, and all 185 patients were HER2 negative.

At diagnosis, 98 patients (53%) of the patients with TNBC were aged between 50–70 years and 61.6% were post-menopausal; 164 (88.6%) patients had a very good ECOG performance status and only 9 (4.9%) patients had a second diagnosis of mammary neoplasm (Table 1). Patients with TNBC were geographically distributed throughout Northern Italy ($n = 82$; 44.3%), Central Italy ($n = 29$; 15.7%) and Southern Italy and the Islands ($n = 74$; 40.0%).

3.1. Tumour characteristics

Of the 185 patients with TNBC, 153 patients (82.7%) had undergone a tumorectomy/quadrantectomy, with the remaining 32 having had a mastectomy. Mean (±SD) size of the primary tumour was 2.1 (±1.1) cm (range 0.1–7.0 cm; median size 1.8 cm; 25th–75th percentile 1.5–2.5 cm) and tumour stage at first diagnosis was subcategorised as pT1mic/pT1a/pT1b/pT1c in 108 patients (58.4%), and pT2/pT3/pT4b in 77 patients (41.6%). The histological type was ductal for 163 patients (88.1%), 5 patients (2.7%) had lobular histotype, 2 patients (1.1%) had both histotypes and 15 patients (8.1%) had other histotypes. One hundred and forty four patients (77.8%) had a highly undifferentiated tumour (G3), 36 patients (19.5%) had a moderately differentiated tumour (G2), 1 patient (0.5%) had a well differentiated tumour (G1) and the differentiation grade was unknown in 4 patients (2.2%).

Sentinel lymph nodes were dissected in 125 patients (67.6%). Dissection of axillary lymph nodes was undertaken in 98 patients (53.0%) and only 40 patients underwent both sentinel lymph node and axillary lymph node dissection. The remaining 58 axillary lymph node dissections were undertaken in patients who had not undergone dissection of sentinel lymph nodes. Two patients did not undergone dissection of lymph nodes. Lymph node staging was stage pN0 (no lymph nodes involved) in 128 patients (69.2%), pN1 (1–3 lymph nodes involved) in 43 patients (23.2%), pN2 (4–9 lymph nodes involved) in 7 patients (3.8%) and pN3 ($\geqslant$10 lymph nodes involved) in 5 patients (2.7%). Lymph node stage was unknown in 2 patients (1.1%).

The Ki67 proliferation index, assessed in 134 patients (72.4%), was $\geqslant$70% in 49 patients (36.6%). The MIB-1 proliferation index, assessed in 49 patients (26.5%), was 0–19% in 11 patients (22.4%), 20–29% in 15 (30.6%) patients and $\geqslant$30 in 23 patients (46.9). The proliferation index was unknown in 2 patients (1.1%). The vascular invasion was positive in 41 patients (22.1%) and negative in 94 patients (50.8%).

3.2. Adjuvant chemotherapy

Most TNBC patients received adjuvant chemotherapy ($n = 179$) (Table 2). An anthracycline with or without a taxane was used in 64 (34.6%) and 87 (47.0%) patients, respectively; 9 patients (4.9%) were treated with a taxane without an anthracycline, and 19 patients (10.3%) received a regimen of cyclophosphamide, methotrexate and fluorouracil (CMF). The most frequently used treatment regimens were doxorubicin or epirubicin + cyclophosphamide (AC/EC) or fluorouracil + epirubicin + cyclophosphamide (FEC); both treatment regimens were followed by docetaxel.

The chemotherapy regimen used in relation to the degree of lymph node involvement is summarised in Table 3. More than 50% of patients ($n = 69$) with no lymph node involvement (pN0) received an anthracycline without a taxane; 33 patients (25.7) received an anthracycline with a taxane. Of 43 patients in stage pN1, 22 patients (51.2%) received an anthracycline with a taxane and 18 patients (41.9%) were treated with an anthracycline without a taxane. The majority of patients with pN2 received an anthracycline with a taxane with the remainder receiving CMF. Of the 5 N3 patients, 3 (60.0%) received an anthracycline with a taxane and 2 (40.0%) received an anthracycline without a taxane.

The mean (±SD) number of chemotherapy cycles performed was 6.3 (±1.9) (range 2–18 cycles; median 6 cycles; 25th–75th percentile 6–8 cycles), which was consistent with the total number of planned cycles of chemotherapy (mean ± SD was 6.5 ± 2.1 cycles; range 3–18 cycles; median 6

Table 1 – Demographic data for the triple-negative breast cancer subgroup.

	n (%)
Total	185 (100)
Mean age at diagnosis (years)	
18–34	8 (4.3)
35–49	53 (28.6)
50–69	98 (53.0)
⩾70	26 (14.1)
ECOG performance status	
0	164 (88.6)
1	18 (9.7)
2	1 (0.5)
3	0
Data missing	2 (1.1)
Menopausal status	
Pre	64 (34.6)
Post	114 (61.6)
Data missing	7 (3.8)
Secondary diagnosis of mammary neoplasm	
Yes	9 (4.9)
No	176 (95.1)
Data missing	
Concomitant disease	
Yes	10 (5.4)
No	175 (94.6)

ECOG, Eastern Cooperative Oncology Group.

Table 2 – Adjuvant treatment in the triple-negative breast cancer subgroup.

	n (%)
Chemotherapy	
CMF	19 (10.3)
Anthracycline without taxane	87 (47.0)
Anthracycline with taxane	64 (34.6)
Taxane without anthracycline	9 (4.9)
None	6 (3.2)
Site of radiotherapy	
Residual breast	138 (74.6)
Chest wall	7 (3.8)
None	40 (21.6)
Hormonal therapy	
None	172 (93.0)
Tamoxifen for 5 years	1 (0.5)
Tamoxifen for 5 years + LHRH agonist	2 (1.1)
Aromatase inhibitors for 5 years	9 (4.9)
LHRH agonist	1 (0.5)
Biological therapy	
None	184 (99.5)
Trastuzumab	1 (0.5)

CMF, cyclophosphamide + fluorouracil + methotrexate; LHRH, luteinizing-hormone-releasing hormone.

cycles; 25th–75th percentile 6–8 cycles). The median duration of chemotherapy was 120 days (range 6–366 days).

Of the 179 patients who received chemotherapy, 12 patients (6.7%) had a chemotherapy dose reduction and 43 patients (24.0%) experienced >7 days delay in treatment, with a median delay in chemotherapy of 10 days (range 7–42 days).

3.3. *Other adjuvant therapies*

One hundred and forty five patients (78.4%) received radiotherapy (Table 2). The main site of radiotherapy was residual breast in 138 patients; 133 patients (91.7%) received external radiation and 5 patients (3.4%) were treated with intraoperative radiation therapy.

In total, 93% of patients did not receive hormonal therapy; 9 of the 13 patients who were given hormonal therapy received aromatase inhibitors for 5 years (Table 2). Similarly, 99.5% of patients did not receive biological therapy; trastuzumab was given to only one patient (0.5%) in clinical practice (Table 2).

4. Discussion

The NEMESI study was an observational, retrospective study undertaken to describe current treatment practices related to the systemic adjuvant treatment of patients with early-stage operable breast cancer in order to improve the knowledge of the therapeutic management of breast cancer in Italy. The current study was focused on the subgroup of patients with TNBC from the NEMESI study.

From a total evaluable population of 1894 patients in the NEMESI study, there were 185 patients with TNBC. Results showed that most patients had undergone a tumorectomy/quadrantectomy and that the mean size of the primary tumour was 2.1 cm. The tumour ductal histotype was predominant and for the majority of patients the tumour was highly undifferentiated. In line with current recommendations,[15,16] some patients underwent axillary lymph node dissection without first having undergone sentinel lymph node biopsy because they had T3 or T4 tumours, or because of the surgeon's choice based on clinical and pathological features of the patient's disease.

All patients with TNBC were treated with adjuvant chemotherapy and/or radiotherapy. Anthracyclines with or without taxanes were the most common types of chemotherapy with AC/EC or FEC followed by docetaxel the most frequently used treatment regimens. Patients with lymph node staging pN0, pN1, pN2, or pN3 were preferentially treated with anthracyclines (without or with taxanes). In total 7% of patients received hormonal therapy and only one patient (0.5%) received biological therapy with trastuzumab. It should be noted that these patients underwent hormonal or biological therapy for various causes; the reasons why they received these therapies were unknown due to the retrospective nature of the study, which guaranteed anonymity when collecting patient data.

Consensus treatment guidelines for the United States recommend adjuvant chemotherapy with anthracycline- and/or taxane-based regimens for the treatment of TNBC,[17] although there is currently no specific chemotherapeutic regimen recommended. For patients with pNO or pN1mi (⩽2 mm axillary node metastasis) with tumuor ⩽1 cm, the guidelines recommend treatment with chemotherapy could be considered (unless the patient is pNO with a tumour ⩽0.5 cm or microinvasive in which case no adjuvant therapy is recommended); for patients with tumour >1 cm and for node-positive patients,

Table 3 – Adjuvant chemotherapy in relation to lymph node stage in the triple-negative breast cancer subgroup.

n (%)	Lymph node stage			
	pN0 *n* = 128	pN1 *n* = 43	pN2 *n* = 7	pN3 *n* = 5
CMF	16 (12.5)	2 (4.7)	1 (14.3)	0
Anthracyclines without taxanes	69 (53.9)	18 (41.9)	0	0
Anthracyclines with taxanes	33 (25.7)	22 (51.2)	6 (85.7)	3 (60.0)
Taxanes without anthracyclines	6 (4.6)	1 (2.3)	0	2 (40.0)
None	6 (4.6)	0	0	0

CMF, cyclophosphamide + fluorouracil + methotrexate.

adjuvant chemotherapy is recommended.[17] Preferred adjuvant regimens (all category 1) include: docetaxel/doxorubicin/cyclophosphamide (TAC); dose-dense AC followed by paclitaxel every 2 weeks; AC followed by weekly paclitaxel; docetaxel and cyclophosphamide (TC); or AC.[17]

The use of taxanes has led to a benefit in the adjuvant treatment in TNBC. The CALGB 9344 trial established the benefit of paclitaxel added to AC, resulting in an increase in disease-free survival and overall survival in this population. The BCIRG 001 trial evaluated the benefit of docetaxel versus fluorouracil when added to doxorubicin and cyclophosphamide (TAC versus FAC).[18–22] Data from a recent retrospective study showed that CMF chemotherapy was effective in triple negative, but only in specific subset node-negative breast cancer.[23]

The St Gallen 2007 Breast Cancer Treatment consensus recommends an anthracycline-containing regimen as the backbone of adjuvant chemotherapy for the treatment of early breast cancer, with 6–8 cycles of chemotherapy generally favored; in the triple-negative setting, anthracycline therapy was endorsed for all patients, although there was only 40% support for taxanes.[24] More recently, the 11th St Gallen conference, held in March 2009, recommended that treatment with adjuvant systemic chemotherapy be the mainstay for patients with triple-negative disease due to the high risk of relapse.[25] Moreover, there is no proven alternative to chemotherapy in triple-negative disease at the present time.[25]

The European Society for Medical Oncology (ESMO) recommends adjuvant chemotherapy for primary breast cancer patients with no detectable expression of ER and PgR who are HER2 negative.[26] Although the optimal duration of chemotherapy is not yet known, the ESMO recommends that chemotherapy be administered for a minimum of four cycles (12–16 weeks), with the aim being treatment for six to eight cycles (18–24 weeks).[26]

In line with current recommendations from the NCCN,[17] the 11th St Gallen conference[25] and the ESMO,[26] this study showed that most patients with TNBC received adjuvant chemotherapy. Notably, all chemotherapy regimens used in this study were standard regimens recommended in the NCCN guidelines.[17]

In this field of research, a subgroup analysis of the pathological characteristics and clinical outcomes of patients with TNBC was performed on data from the National Oncological Research survey on adjuvant therapy in breast cancer (NORA),[27] a prospective, longitudinal cohort study investigating treatment and clinical outcomes in patients with operable early breast cancer treated in Italy in over 70 oncology centres from 2000 to 2004.[28] The NORA subgroup analysis showed that 123 out of 2968 (4.1%) evaluable patients had TNBC.[27] Similar to our study, 61.7% of patients with TNBC in the NORA study were treated with conservative surgery, 55.3% had T1, 47.9% were pN+ and 63.2% had a highly undifferentiated tumour (G3).[27] Although 89.4% of TNBC patients in the NORA study were treated with chemotherapy, this was anthracycline-based for only 54.1% of patients.[27] In contrast, the current study demonstrated that 81.6% of TNBC patients received anthracycline-based therapy; the increased number of patients receiving anthracycline-based therapy may reflect changes in current clinical practice in concordance with current recommendations. It is important to note that, in the years separating the NORA and NEMESI studies, the ability to identify the specific subgroup of patients with TNBC has improved.

Limited clinical evidence suggests that TNBC may be more chemosensitive than other phenotypes (i.e. *ER*- and HER2-positive), despite poorer overall survival.[29] This observation is supported by several studies conducted in the neoadjuvant setting. Several studies have demonstrated that TNBC has significantly higher pathologic complete response (pCR) rates when treated with neoadjuvant chemotherapy and that pCR correlates well with improved outcomes.[3,7,20,30]

The failure of conventional treatment in patients with TNBC results in a more aggressive relapse with worse overall survival.[3] Studies are ongoing in the assessment of existing and novel adjuvant therapies in the triple-negative setting. There are also several ongoing trials in the adjuvant setting of TNBC which are evaluating the role of novel anti-tubulin agents such as ixabepilone, and anti-angiogenic agents such as bevacizumab.[2] In addition, other agents (including epidermal growth factor receptor and poly ADP-ribose polymerase inhibitors) are currently under investigation in TNBC and have shown promising results in the treatment of this aggressive subtype in the metastatic setting.[3] There is also interest in DNA-damaging agents such as platinum compounds as potential treatment options in TNBC.[3] Hence, it is important to understand the underlying molecular mechanisms of TNBC in conjunction with the development of specifically targeted treatments.

Although the current study is limited by its retrospective, observational nature, the data shown here provide an overview of current clinical practice in the treatment of TNBC in Italy.

In conclusion, this study provides important information on current clinical practice in the use of adjuvant therapies

for the treatment of early-stage breast cancer, and on factors that may influence the treatment decision and the choice of treatment regimens in the National Italian territory. Overall, the results of this study indicate a satisfactory level of adherence of Italian clinical practice to International Guidelines in the management of early-stage TNBC.

Conflict of interest statement

The authors have no conflicts of interest that are directly relevant to the content of this article.

DD is a full time employee of Sanofi-Aventis.

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