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Adjuvant treatment of early breast cancer: do the St Gallen recommendations influence clinical practice? Results from the NORA study

M. E. Cazzaniga[1]*, G. Mustacchi[2], P. Pronzato[3], A. De Matteis[4], F. Di Costanzo[5] & I. Floriani[6]
On behalf of the NORA Study Group

[1]*Medical Oncology, Treviglio Hospital, Treviglio;* [2]*Medical Oncology Department, University of Trieste, Trieste;* [3]*Medical Oncology, IST, Genova;* [4]*Medical Oncology C, Istituto Pascale, Napoli;* [5]*Medical Oncology, Ospedale Careggi, Firenze;* [6]*Oncology Department, Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy*

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Background: The NORA study is a prospective longitudinal cohort study aiming at investigating treatment in patients with early breast cancer. Here, we present the impact of the St Gallen recommendations on clinical practice.
Patients and methods: We compared adjuvant strategies in patients enrolled in 2000–2002 to those in 2003–2004 to verify the impact of the 2003 St Gallen recommendations.
Results: The use of aromatase inhibitors (AIs) doubled: 65/629 patients (10.3%) vs 100/458 patients (21.8) ($P < 0.0001$). Following chemotherapy, AIs were administered in 8.5% of the retrospective cohort and in 15.1% of the prospective one ($P < 0.0001$). The use of taxanes plus hormones dropped ($P = 0.0026$), but not when used as single agents. A marked increase was observed in the use of anthracycline-based chemotherapy (46.3% vs 65.2%), mainly three-drug regimens (33.3% vs 46.6%).
Conclusion: Our results suggest that the St Gallen recommendations have had a major impact on clinical practice.
Key words: adjuvant therapy, breast cancer, St Gallen recommendations

introduction

Adjuvant treatment of early breast cancer is one of the most controversial areas in the field of solid tumour therapy. The rapid evolution of research in this area renders the appropriate application of new findings in clinical practice a difficult task. Different guidelines are available concerning adjuvant strategies that could be applied in the treatment of early breast cancer [1–3]. Each strives to summarize recent findings from clinical research and release practical recommendations to clinicians.

In Europe, the most representative set of guidelines are those released by the panelists of the St Gallen Consensus Conference, which takes place every 2 years. The series of conferences held in St Gallen since 1978 has specifically focused on reaching expert consensus on the implications of evidence for treatment selection. Nevertheless, the real application of the conference recommendations in clinical practice is not known.

The NORA (National Oncological Research observatory on Adjuvant therapy in breast cancer) study was designed to obtain information regarding adjuvant strategies applied in completely resected breast cancer patients. The main focus of NORA is the description of factors that may play a leading part in treatment choice. Secondary aims include description of the possible choices of following treatments; assessment of the extent by which treatment patterns observed in clinical practice conform to international breast cancer treatment guidelines; and patient outcome in terms of disease-free survival (DFS), site of relapse and overall survival (OS).

The 2003 St Gallen Consensus Conference clarified some new findings coming from several recently completed clinical trials. The ATAC (Arimidex, Tamoxifen Alone or in Combination) trial [4] has shown preliminary evidence that anastrozole is superior to tamoxifen as adjuvant therapy for postmenopausal patients, 84% of whom had disease recorded as receptor-positive. The American Society of Clinical Oncologists' (ASCO) technology assessment [5] report has recommended that anastrozole be used only in patients in whom tamoxifen is contraindicated or not tolerated. The St Gallen panel endorsed this position.

For premenopausal women with endocrine-responsive disease, ovarian function suppression (goserelin) with [6] or without [7] tamoxifen appeared to be at least as effective as

Correspondence to: Marina E. Cazzaniga, Medical Oncology, Ospedale di Treviglio, P. le Ospedale 1, 24047 Treviglio (BG), Italy. Tel: +39-0363424303; Fax: +39-0363424380; E-mail: oncologia@tin.it

CMF chemotherapy alone. The combination of tamoxifen and GnRH analogues was more effective than GnRH analogues alone, at least in the presence of chemotherapy [8].

Two major trials examined four courses of paclitaxel after four cycles of AC. However, the interpretation of their results was made difficult by the confounding effects of factors such as treatment duration, receptor status and the concurrent administration of tamoxifen [9, 10]. In the recent BCIRG trial [11], TAC (docetaxel, doxorubicin, cyclophosphamide) proved superior to FAC (5-fluorouracil, doxorubicin, cyclophosphamide). Over 20000 women have been included in additional randomized clinical trials investigating the role of taxanes, which have yet to report results.

In this article, we analyse the impact of the St Gallen guidelines released at the very beginning of 2003 on clinicians' choices of adjuvant treatment for early breast cancer patients, focusing on aromatase inhibitors (AIs) in postmenopausal women, LHRH analogues in premenopausal patients and the use of taxanes and anthracyclines in node-positive women.

patients and methods

The NORA survey is a longitudinal multicentre observational cohort study. Participating oncology centres include both academic and non-academic institutions, distributed across Italy and representative of the national situation. Each centre was asked to register data of the first 10 consecutive patients treated in the years 2000, 2001 and 2002 (retrospective cohort), as well as of the first 20 consecutive patients who reached the oncology unit in 2003 (prospective cohort), for a total of at least 50 patients for each centre. These criteria were selected with the aim of maximizing enrolment, while shortening the time needed to obtain an adequate follow-up period and allow a suitable coverage of patient enrolment time. The two cohorts were well balanced in terms of TN stage, grading and hormone receptor status.

Inclusion criteria were first diagnosis of invasive breast cancer and absence of metastatic disease. Women affected by in situ carcinoma alone or who had undergone surgery with palliative intent (macroscopic residual disease) were considered ineligible. Concomitant participation in a clinical study did not qualify as an exclusion criterion, as long as the proportion of these patients remained below 20% and 40% in the retrospective and prospective cohorts, respectively. Data were collected concerning demographic characteristics, family and pathological history and diagnostic methods, as well as information on surgery, pathological features and adjuvant treatments. Data collection on changes in adjuvant treatment, on toxicity and on cancer-related events is also planned. For this purpose, all patients had to be followed for a minimum of 4 years and a maximum of 8 years, at 6-month intervals.

The study complied with the requirements of Italian law regarding observational studies. The nature and purposes of the survey were explained in detail to all potential participants, and their consent to data handling according to Italian regulations on privacy was obtained.

Assuming involvement of approximately 70 centres with a minimum recruitment of 50 patients, it was planned to enrol a total of approximately 3500 women. This number allows us to obtain an estimate of the distribution of adjuvant strategies with a 95% confidence interval (CI) width of 3% at most.

We compared adjuvant strategies implemented in the retrospective cohort (patients diagnosed and treated in the period 2000–2002) with those chosen for the prospective cohort (2003–2004) to assess the impact of new recommendations released by the St Gallen Consensus Conference on clinical practice held in March 2003. This cut-off time for analysis was chosen in consideration of the fact that most patients in the prospective cohort were enrolled as of the second trimester of 2003, after all local ethical committees had approved the study and the St Gallen Consensus Conference had taken place. Even though the 2003 recommendations were released via online advanced access only in July and as a full paper in September, most of the data presented would have been available within 2–3 weeks of the meeting by different means.

results

A total of 3532 breast cancer patients was enrolled by 71 Italian centres. Subsequently 17 patients (0.5%) were excluded due to the presence of synchronous tumours and 3515 patients were eligible for analysis. Academic institutions represented 21.2% of the centres; 42.3% were located in northern Italy, 28.2% in central Italy and 29.6% in southern Italy and the islands. Therefore, institutions were evenly distributed in terms of both their type and geographical distribution and were considered representative of the national situation. The retrospective cohort included 2075 women (59%); 669 (32.2%) were enrolled in 2000, 697 (33.6%) in 2001 and 709 (34.2%) in 2002. Most patients in the prospective cohort (1146, 79.6%) were enrolled after the second trimester of 2003, as shown in Figure 1 and Table 1. The majority of local ethical committees gave their approval at the end of February, so we can assume that patients enrolled in the first trimester of 2003 were those observed mainly during March. Baseline characteristics and pathological features of the entire population have been reported in a previous paper [12] and are briefly summarized in Table 2.

In the retrospective cohort 15 patients (0.7%) received no adjuvant treatment, and 32 patients (1.5%) underwent only radiotherapy (RXT) without any systemic therapy. Adjuvant treatment without RXT was administered in 757 cases (36.5%), while the remaining 1270 (61.2%) received systemic treatment plus RXT. In the prospective cohort, there were 11 patients without any treatment (0.8%) and 15 were treated with RXT only (1.0%). In 1412 patients (98.1%) systemic adjuvant treatment was administered, either alone (460, 31.9%) or with RXT (952, 66.1%).

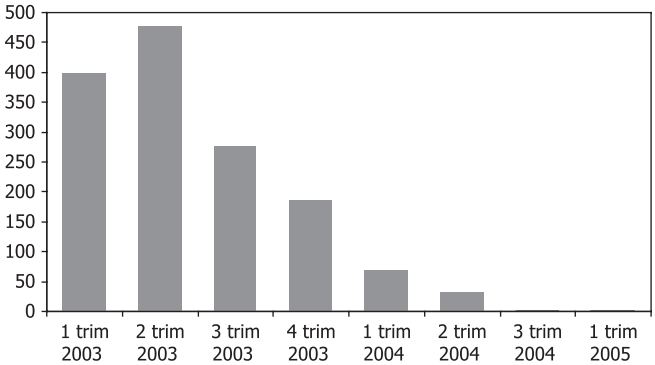

Figure 1. Enrolment of patients in the prospective cohort by trimester.

Table 1. Enrolment of patients in the prospective cohort by trimester

Trimester and year	No.
T1 2003 (March 2003)	399
T2 2003	477
T3 2003	276
T4 2003	186
T1 2004	71
T2 2004	32
T3 2004	1
T1 2005	1

T, trimester.

Table 2. Main biological characteristics of the two cohorts

Parameter	Retrospective	%	Prospective	%
pT stage				
T1	1228	58.7	865	41.3
T2	715	59.6	485	40.4
T3	51	53.1	45	46.9
T4	73	63.5	42	36.5
Missing	8		5	
pN stage				
N0	1153	59.8	776	40.2
N+	885	57.8	645	42.2
Nx	37	1.7	19	1.3
Grading				
G1	273	60.4	179	39.6
G2	957	58.8	671	41.2
G3	633	58.0	459	42.0
ND	214		131	
Oestrogen receptor status				
+	1605	58.2	1151	41.8
–	417	60.5	272	39.5
Unknown	35		12	
Progesterone receptor status				
+	1331	57.2	996	42.8
–	670	63.3	389	36.7
Unknown	72		55	

No significant differences have been observed between the two cohorts in terms of choice of strategy: chemotherapy (CHT) followed by endocrine therapy (HT) was the preferred strategy, having been chosen in 1000 out of 2027 patients of the retrospective cohort (49.3%) and in 701 out of 1440 patients (49.6%) of the prospective group. The distribution of adjuvant treatment options is reported in Table 3.

Concerning endocrine therapy, the use of AIs doubled after the release of the St Gallen guidelines from 65 out of 629 patients (10.3%) in the retrospective group to 100 out of 458 patients (21.8%) in the prospective group ($\chi^2 = 27.2$, $P < 0.0001$). Following CHT, AIs were administered in 8.5% of the retrospective cohort and in 15.1% of the prospective cohort ($\chi^2 = 16.3$, $P < 0.0001$).

LHRH analogues alone were used in 0.2% and 0.7% of patients in the retrospective and prospective groups, respectively. LHRH analogues with tamoxifen or AIs were administered in 36 out of 629 retrospective cohort patients (5.7%) and 42 out of 458 in the prospective cohort (9.2%) ($\chi^2 = 4.7$, $P = 0.0298$).

Concerning the choice of taxane-based CHT, no substantial difference was observed between the two groups when taxanes were administered alone. In particular, 19 out of 393 oestrogen receptor-negative patients (4.8%) and 16 out of 253 patients (6.3%) in the retrospective and prospective cohort respectively were treated with taxanes alone ($\chi^2 = 0.67$, $P = 0.4147$). Nevertheless, analysis of the use of taxanes in patients treated with chemotherapy followed by endocrine therapy (most were oestrogen receptor-positive) revealed a marked decrease in the choice of these drugs: 60 out of 1000 (6.0%) in the retrospective population and 20 out of 701 (2.9%) in the prospective one ($\chi^2 = 9.1$, $P = 0.0026$).

Prescription of anthracycline-based CHT when CHT alone was the chosen strategy registered a significant increase from 46.3% to 65.2%, mostly concerning the use of three-drug regimens such as FEC and FAC (131/393, 33.3% vs 118/253, 46.6%). Finally, no significant difference was observed in the use of combination therapy with endocrine drugs (anthra-3: 37.1% vs 43.1%; anthra-2: 10.2% vs 15.9%), as reported in Table 4.

discussion

The aim of the present sub-study was to assess the impact of the latest St Gallen guidelines on clinical practice, by comparing the choice of selected treatments administered to patients before and after the release of the guidelines. The choice in favour of sequential chemotherapy and endocrine therapy did not significantly change in the prospective cohort in comparison to the retrospective one, despite the panelists' confirmation that endocrine therapy alone is a valid alternative.

Concerning AIs, endorsement by the panelists of the ASCO technology assessment suggestions promptly led to the introduction of these drugs in clinical practice, even though approval of their use in the adjuvant setting by the Italian regulatory office had only been received the following year. It is probable that the urgent need for new endocrine agents, coupled with the encouraging results of the ATAC trial, reassured clinicians regarding the safety of their use in the early stages of disease.

The use of taxanes, especially in combination with CHT, dropped dramatically as a result of the St Gallen recommendations. Preliminary results of large randomized trials presented at different international meetings [9, 10] in the late 1990s probably encouraged oncologists to experiment with taxanes in high-risk patients. It is noteworthy that taxanes were almost dismissed in patients who were also receiving endocrine therapy, while their use as single agents has not registered significant differences. With all probability, the availability of robust evidence in favour of endocrine therapy, together with the difficulty of

Table 3. Adjuvant strategies in the retrospective and prospective cohorts

Adjuvant treatment	Retrospective	%	Prospective	%
HT	629	31	458	32.4
CHT	393	19.4	253	17.9
CHT + HT	1000	49.3	701	49.6

CHT, chemotherapy; HT, endocrine therapy.

Table 4. Administration of AIs, LHRH analogues, taxanes and anthracyclines in the retrospective and prospective cohorts

Adjuvant treatment	Retrospective	%	Prospective	%	*P* value
HT alone	629		458		
Aromatase inhibitors	65	10.3	100	21.8	<0.0001
LHRH analogues	1	0.2	3	0.7	
TAM/AIs + LHRH	36	5.7	42	9.2	0.0298
CHT alone	393		253		
Anthra-2 drugs	51	13.0	47	18.6	
Anthra-3 drugs	131	33.3	118	46.6	
Taxanes	19	4.8	16	6.3	0.4147
CHT + HT	1000		701		
Anthra-2 drugs + HT	102	10.2	112	15.9	
Anthra-3 drugs + HT	371	37.1	302	43.1	
Taxanes + HT	60	6.0	20	2.9	0.0026

CHT, chemotherapy; HT, endocrine therapy.

interpreting the data coming from the taxane study, pushed oncologists to abandon the latter in combination with endocrine therapy but to maintain them when the combination with new potent endocrine drugs is not indicated, as is the case with oestrogen receptor-negative patients.

The use of LHRH analogues did not register great changes, despite the publication of important favourable clinical trial results [5–8]. This finding could be attributable to the fact that the vast majority of patients were menopausal (72.3%) at the moment of study enrolment: the small number of young patients could have prevented the detection of any potential changes.

The attitude of Italian oncologists towards the use of anthracyclines in the adjuvant setting markedly changed after the release of the guidelines. An audit of clinical practice conducted in Italy in the early months of 2000 [13] reported that CMF was administered in 60% of cases, while anthracyclines used as single agents accounted only for 34% (adryamicin) and 45% (epirubicin) of patients.

We can speculate that the early diffusion of the recommendations and the vast participation in the meeting by oncologists are the most likely reasons for the differences observed. Our results suggest a good reception of international guidelines by Italian oncologists. In particular, the St Gallen Consensus Conference seems to have had a great impact in clinical practice.

co-Authors

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