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Original Research

Dose-dense adjuvant chemotherapy in premenopausal breast cancer patients: A pooled analysis of the MIG1 and GIM2 phase III studies

Matteo Lambertini [a,b], Marcello Ceppi [c], Francesco Cognetti [d], Giovanna Cavazzini [e], Michele De Laurentiis [f], Sabino De Placido [g], Andrea Michelotti [h], Giancarlo Bisagni [i], Antonio Durando [j], Enrichetta Valle [k], Tiziana Scotto [l], Andrea De Censi [m], Anna Turletti [n], Marco Benasso [o], Sandro Barni [p], Filippo Montemurro [q], Fabio Puglisi [r], Alessia Levaggi [s], Sara Giraudi [s], Claudia Bighin [a], Paolo Bruzzi [c], Lucia Del Mastro [s,*] for the MIG and GIM study groups[1]

[a] *Department of Medical Oncology, U.O. Oncologia Medica 2, IRCCS AOU San Martino – IST, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy*
[b] *Department of Medicine, BrEAST Data Centre, Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Brussels, Belgium*
[c] *Epidemiology Unit, IRCCS AOU San Martino – IST, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy*
[d] *Department of Medical Oncology, Istituto Regina Elena per lo Studio e la Cura dei Tumori, Roma, Italy*
[e] *Medical Oncology, Azienda Ospedaliera Carlo Poma, Mantova, Italy*
[f] *Medical Oncology, Istituto Nazionale Tumori-IRCCS Fondazione Pascale, Napoli, Italy*
[g] *Medical Oncology, Azienda Ospedaliera Universitaria Federico II, Napoli, Italy*
[h] *UO Oncologia Medica I, Ospedale S. Chiara, Dipartimento di oncologia, dei trapianti e delle nuove tecnologie, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*
[i] *Medical Oncology, IRCCS Arcispedale S. Maria Nuova, Reggio Emilia, Italy*
[j] *Breast Unit, Azienda Ospedaliera Universitaria Città della Salute e delle Scienze, Torino, Italy*
[k] *Medical Oncology, ASL8-Ospedale Oncologico A. Businco, Cagliari, Italy*
[l] *U.O. Oncologia Medica, Ospedale Civile, Sassari, Italy*
[m] *S.C. Oncologia Medica, Medical Oncology Unit, E.O. Ospedali Galliera, Genova, Italy*
[n] *Medical Oncology, ASLTO1, Torino, Italy*
[o] *Medical Oncology, Ospedale San Paolo, Savona, Italy*
[p] *Medical Oncology, Azienda Ospedaliera, Caravaggio, Treviglio, Bergamo, Italy*

* *Corresponding author*: Department of Medical Oncology, U.O. Sviluppo Terapie Innovative, IRCCS AOU San Martino – IST, Istituto Nazionale per la Ricerca sul Cancro, Largo Rosanna Benzi, 10, 16132, Genova, Italy. Fax: +39 010 5556383.
E-mail addresses: matteo.lambertini85@gmail.com (M. Lambertini), marcello.ceppi@hsanmartino.it (M. Ceppi), cognetti@ifo.it (F. Cognetti), mariagiovanna.cavazzini@aopoma.it (G. Cavazzini), delauren@unina.it (M. De Laurentiis), deplacid@unina.it (S. De Placido), a.michelotti@ao-pisa.toscana.it (A. Michelotti), bisagni.giancarlo@asmn.re.it (G. Bisagni), andurando63@gmail.com (A. Durando), enrichettavalle@asl8cagliari.it (E. Valle), scotto.tiziana@libero.it (T. Scotto), andrea.decensi@galliera.it (A. De Censi), annaturletti@virgilio.it (A. Turletti), m.benasso@asl2.liguria.it (M. Benasso), sandro.barni@ospedale.treviglio.bg.it (S. Barni), filippo.montemurro@ircc.it (F. Montemurro), fabio.puglisi@uniud.it (F. Puglisi), alessia.levaggi@hsanmartino.it (A. Levaggi), sara.giraudi@hsanmartino.it (S. Giraudi), claudia.bighin@hsanmartino.it (C. Bighin), paolo.bruzzi@hsanmartino.it (P. Bruzzi), lucia.delmastro@hsanmartino.it (L. Del Mastro).
[1] Written on behalf of the Mammella InterGruppo (MIG) and the Gruppo Italiano Mammella (GIM) study groups.

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[q] Investigative Clinical Oncology, Fondazione del Piemonte per l'Oncologia/Candiolo Cancer Center (IRCCS), Candiolo, Torino, Italy
[r] Department of Oncology, Azienda Ospedaliera di Udine, Udine, Italy
[s] Department of Medical Oncology, U.O. Sviluppo Terapie Innovative, IRCCS AOU San Martino – IST, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy

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Abstract ***Background:*** No evidence exists to recommend a specific chemotherapy regimen in young breast cancer patients. We performed a pooled analysis of two randomised clinical trials to evaluate the efficacy of adjuvant dose-dense chemotherapy in premenopausal breast cancer patients and its impact on the risk of treatment-induced amenorrhoea.
Patients and methods: In the MIG1 study, node-positive or high-risk node-negative patients were randomised to 6 cycles of fluorouracil/epirubicin/cyclophosphamide every 2 (dose-dense) or 3 (standard-interval) weeks. In the GIM2 study, node-positive patients were randomised to 4 cycles of dose-dense or standard-interval EC or FEC followed by 4 cycles of dose-dense or standard-interval paclitaxel. Using individual patient data, the hazard ratio (HR) for overall survival by means of a Cox proportional hazards model and the odds ratio for treatment-induced amenorrhoea through a logistic regression model were calculated for each study. A meta-analysis of the two studies was performed using the random effect model to compute the parameter estimates.
Results: A total of 1,549 patients were included. Dose-dense chemotherapy was associated with a significant improved overall survival as compared to standard-interval chemotherapy (HR, 0.71; 95% confidence intervals [CI], 0.54–0.95; p = 0.021). The pooled HRs were 0.78 (95% CI, 0.54–1.12) and 0.65 (95% CI, 0.40–1.06) for patients with hormone receptor-positive and -negative tumours, respectively (interaction p = 0.330). No increased risk of treatment-induced amenorrhoea was observed with dose-dense chemotherapy (odds ratio, 1.00; 95% CI, 0.80–1.25; p = 0.989).
Conclusion: Dose-dense adjuvant chemotherapy may be considered the preferred treatment option in high-risk premenopausal breast cancer patients.

1. Introduction

In women of reproductive age, breast cancer is the most common tumour type and the leading cause of cancer-related deaths [1]. The majority of young women with early-stage breast cancer are candidates to receive an anticancer treatment that includes chemotherapy [2]. However, to date, there is no evidence to recommend a specific chemotherapy regimen in this subgroup of patients [2]. The identification of the optimal chemotherapy regimen for young women regarding efficacy and long-term tolerance is considered a research priority [3].

A possible side-effect of chemotherapy in premenopausal women is the occurrence of treatment-induced amenorrhoea [4]. The loss of ovarian function negatively impacts on global health of young breast cancer survivors being associated with several side-effects and infertility [5,6]. Failure to address these concerns and intervene in a timely manner can negatively affect not only patients' quality of life but also their adherence to treatment and subsequent disease outcomes [1].

Dose-dense adjuvant chemotherapy has become a mainstay adjuvant treatment for high-risk breast cancer patients [7,8]. Although no heterogeneity of the effect of dose-dense chemotherapy according to menopausal status at diagnosis has been previously observed, no specific data exist on the efficacy of this schedule in premenopausal women. In addition, there are very limited and retrospective data on the impact of dose-dense chemotherapy on the risk of developing treatment-induced amenorrhoea [9,10]. In the present study, we performed a pooled analysis restricted to premenopausal patients of the MIG1 (Mammella InterGruppo 1) and GIM2 (Gruppo Italiano Mammella 2) adjuvant trials [11,12], to investigate the efficacy of dose-dense schedule in this specific patient population and its impact on the risk of treatment-induced amenorrhoea.

2. Patients and methods

2.1. Study design and participants

This study combined individual patient data from premenopausal patients enrolled in the MIG1 and GIM2 studies that were designed independently to determine the impact of dose-dense chemotherapy in the adjuvant treatment of women with operable node-positive or high-risk node-negative invasive breast cancer.

In the multicenter, open-label, phase III, randomised MIG1 study, eligible patients were women aged 18–70 years with histologically confirmed breast cancer who had undergone radical surgery, and with node-positive (≤10 involved lymph nodes) or high-risk node-negative (defined by the presence of ≥1 following criteria: age ≤ 35 years, hormone receptor-negative status, tumour size ≥ 2 cm, poor histologic grade and/or high proliferative rate) disease [11].

In the multicenter, open-label, phase III, randomised GIM2 study, eligible patients were women aged 18–70 years with histologically confirmed breast cancer who had undergone radical surgery and with histological evidence of tumour in at least one axillary lymph node [12].

For the purpose of the present pooled analysis, only patients who were premenopausal before randomisation were included. Premenopausal status was defined by presence of regular menses in the prior 6 or 12 months before the initiation of chemotherapy in the MIG1 and GIM2 studies, respectively [11,12].

The MIG1 and GIM2 studies were conducted at 21 and 81 Italian centres, respectively. The Institutional Review Boards of all the participating centres approved the MIG1 and GIM2 study protocols. All patients enrolled in the trials provided written informed consent before study entry. The trials were conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

2.2. Procedures

In the MIG1 study, eligible patients were randomly assigned in a 1:1 ratio to receive 6 courses of 5-fluorouracil, epirubicin and cyclophosphamide (FEC, 600/60/600 mg/m^2) administered every 2 (i.e. dose-dense arm) or every 3 (i.e. standard-interval arm) weeks [11]. To support dose-dense schedule, filgrastim at a dose of 5 μg/kg of body weight/day from day 4–11 after chemotherapy was mandatory. The two stratification factors at randomisation were nodal status (0 versus ≥1 positive nodes) and centre.

In the GIM2 study, eligible patients were randomly allocated in a 1:1:1:1 ratio to one of the following 4 study arms: (a) dose-dense FEC-P, (b) dose-dense EC-P, (c) standard-interval FEC-P and (d) standard-interval EC-P [12]. The dose per cycle of epirubicin (90 mg/m^2), cyclophosphamide (600 mg/m^2) and paclitaxel (P, 175 mg/m^2) was the same in all the arms; in arms a and c, the dose of fluorouracil was 600 mg/m^2. To support dose-dense schedule, subcutaneous pegfilgrastim 6 mg 24–72 h after chemotherapy was mandatory [13]. Centre was the only stratification factor at randomisation [12].

In both studies, women with hormone receptor-positive disease (i.e. defined as at least 10% of positive cells by immunohistochemical analysis) received adjuvant endocrine therapy [11,12].

2.3. Objectives and endpoints

The primary endpoint of the MIG1 study was overall survival (OS); secondary endpoints included toxicity and event-free survival [11]. The two primary comparisons of the GIM2 study were between FEC-P and EC-P, and between dose-dense and standard-interval chemotherapy: the primary endpoint was disease-free survival; secondary endpoints included OS and safety [12].

The main objectives of the present pooled analysis were to investigate the efficacy of dose-dense schedule in premenopausal patients and to assess the impact of dose-dense chemotherapy on the risk of treatment-induced amenorrhoea. The study endpoints were OS and incidence of treatment-induced amenorrhoea comparing between patients treated with dose-dense chemotherapy and women receiving standard-interval chemotherapy. For the purpose of the present analysis, within the GIM2 study, dose-dense FEC-P and dose-dense EC-P arms were considered together (i.e. dose-dense arm), as well as standard-interval FEC-P and standard-interval EC-P (i.e. standard-interval arm).

2.4. Statistical analyses

Sample size calculations and statistical assumptions on the primary objective of each study were previously described [11,12].

The present analyses were conducted according to a pre-planned protocol (Supplementary Material). OS was defined as the time interval between the date of randomisation and the date of death from any cause or loss to follow-up; observation times of patients known to be alive without events at the last follow-up were censored. In the MIG1 study, treatment-induced amenorrhoea was defined by the absence of menses for at least 3 months during chemotherapy or within 3 months after the end of chemotherapy according to the current definition adopted at that time [14]. In the GIM2 study, treatment-induced amenorrhoea was defined according to the World Health Organisation definition of postmenopausal status as absence of menses for ≥12 months after the end of chemotherapy [15].

Median period of follow-up and its interquartile range (IQR) were calculated according to the reverse Kaplan–Meier method. OS probability was computed according to the Kaplan–Meier method; confidence intervals (CI) of survival time probability were calculated according to the log–log method. As estimates of treatment effect, hazard ratio (HR) with 95% CI were calculated with the Cox proportional hazards model adjusting by age, number of lymph nodes, grading and hormone receptors. The risk of treatment-induced amenorrhoea was computed by applying the logistic regression model. Odds ratio (OR) with 95% CI were calculated to estimate the treatment effect adjusting by a suitable set of confounders. In this analysis, only patients with available information on treatment-induced amenorrhoea were included.

Individual patient data for all premenopausal women enrolled in the MIG1 and GIM2 studies were retrieved, and the study endpoints were calculated in each study. A meta-analysis of the two studies was then performed; the random effect model was used to compute the parameter estimates [16]. Subgroup analyses of OS were performed through a meta-regression model and the consistency of the treatment effect on the outcome according to hormone receptor status (positive and negative) was assessed by means of the *t*-test statistic modified by Knapp and Hartung [17].

All reported statistical analyses were based on the study intention-to-treat population. All statistical tests were 2-sided, and p values less than 0.05 were considered statistically significant.

Statistical analyses were performed using STATA 13.1 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

3. Results

Between November 1, 1992 and June 30, 1997, a total of 1,214 patients entered the MIG1 study and 528 were premenopausal at study entry (Fig. 1A). Between April 24, 2003 and July 3, 2006, 2,091 patients entered the GIM2 study and 1,021 were premenopausal at study entry (Fig. 1B). Thus, 1,549 premenopausal patients were included in the present pooled analysis: 762 women underwent dose-dense chemotherapy and 787 standard-interval chemotherapy (Fig. 1).

Median follow-up time was 11.3 years (IQR, 7.6–16.8 years) in the MIG1 study and 6.9 years (IQR, 5.7–7.7 years) in the GIM2 study. The treatment arms of both studies were well balanced with respect to demographic and tumour characteristics (Table 1).

3.1. Dose-dense chemotherapy and OS

In the MIG1 study, 10-year OS was 84.9% (95% CI, 80.4–89.4) in the dose-dense arm and 79.1% (95% CI, 74.0–84.2) in the standard-interval arm (HR, 0.72; 95% CI, 0.47–1.11; p = 0.137; Fig. 2A). In the GIM2 study, 10-year OS was 88.0% (95% CI, 84.3–91.7) in the dose-dense arm and 77.3% (95% CI, 69.1–85.5) in the standard-interval arm (HR, 0.71; 95% CI, 0.48–1.04; p = 0.079; Fig. 2B). The pooled analysis showed that dose-dense chemotherapy was associated with a significant improvement in OS as compared with standard-interval chemotherapy (HR, 0.71; 95% CI, 0.54–0.95; p = 0.021; I^2 = 0.0%, $p_{heterogeneity}$ = 0.953; Fig. 2C).

In patients with hormone receptor-positive disease, 10-year OS was 86.1% (95% CI, 80.6–91.6) in the dose-dense arm and 83.5% (95% CI, 77.2–89.8) in the standard-interval arm in the MIG1 study (HR, 0.85; 95% CI, 0.46–1.57), and 88.9% (95% CI, 85.0–92.8) in the dose-dense arm and 77.2% (95% CI, 66.8–87.6) in the standard-interval arm in the GIM2 study (HR, 0.74; 95% CI, 0.47–1.17). In patients with hormone receptor-negative disease, 10-year OS was 81.1% (95% CI, 72.7–89.5) in the dose-dense arm and 72.2% (95% CI, 63.0–81.4) in the standard-interval arm in the MIG1 study (HR, 0.67; 95% CI, 0.35–1.30), and 83.2% (95% CI, 73.4–93.0) in the dose-dense arm and 74.1% (95% CI, 64.1–84.1) in the standard-interval arm in the GIM2 study (HR, 0.62; 95% CI, 0.29–1.31). The pooled HRs were 0.78 (95% CI, 0.54–1.12; I^2 = 0.0%, $p_{heterogeneity}$ = 0.734) and 0.65 (95% CI, 0.40–1.06; I^2 = 0.0%, $p_{heterogeneity}$ = 0.856) for patients with hormone receptor-positive and -negative tumours, respectively (interaction p = 0.330; Fig. 2D).

3.2. Dose-dense chemotherapy and treatment-induced amenorrhoea

A total of 34 (6.4%) patients in the MIG1 study and 119 (11.7%) in the GIM2 study were not evaluable for incomplete information on treatment-induced amenorrhoea (Fig. 1).

In the MIG1 study, 140 (56.9%) patients developed treatment-induced amenorrhoea in the dose-dense arm and 140 (56.5%) in the standard-interval arm (OR, 1.13; 95% CI, 0.77–1.65; p = 0.532). In the GIM2 study, 190 (43.0%) patients developed treatment-induced amenorrhoea in the dose-dense arm and 201 (43.7%) in the standard-interval arm (OR, 0.94; 95% CI, 0.72–1.24; p = 0.670). The pooled analysis showed that dose-dense chemotherapy was not associated with an increased risk of treatment-induced amenorrhoea (OR, 1.00; 95% CI, 0.80–1.25; p = 0.989; I^2 = 0.0%, $p_{heterogeneity}$ = 0.450; Fig. 3).

4. Discussion

In the present pooled analysis including all premenopausal patients enrolled in two phase III adjuvant trials, dose-dense chemotherapy was associated with a

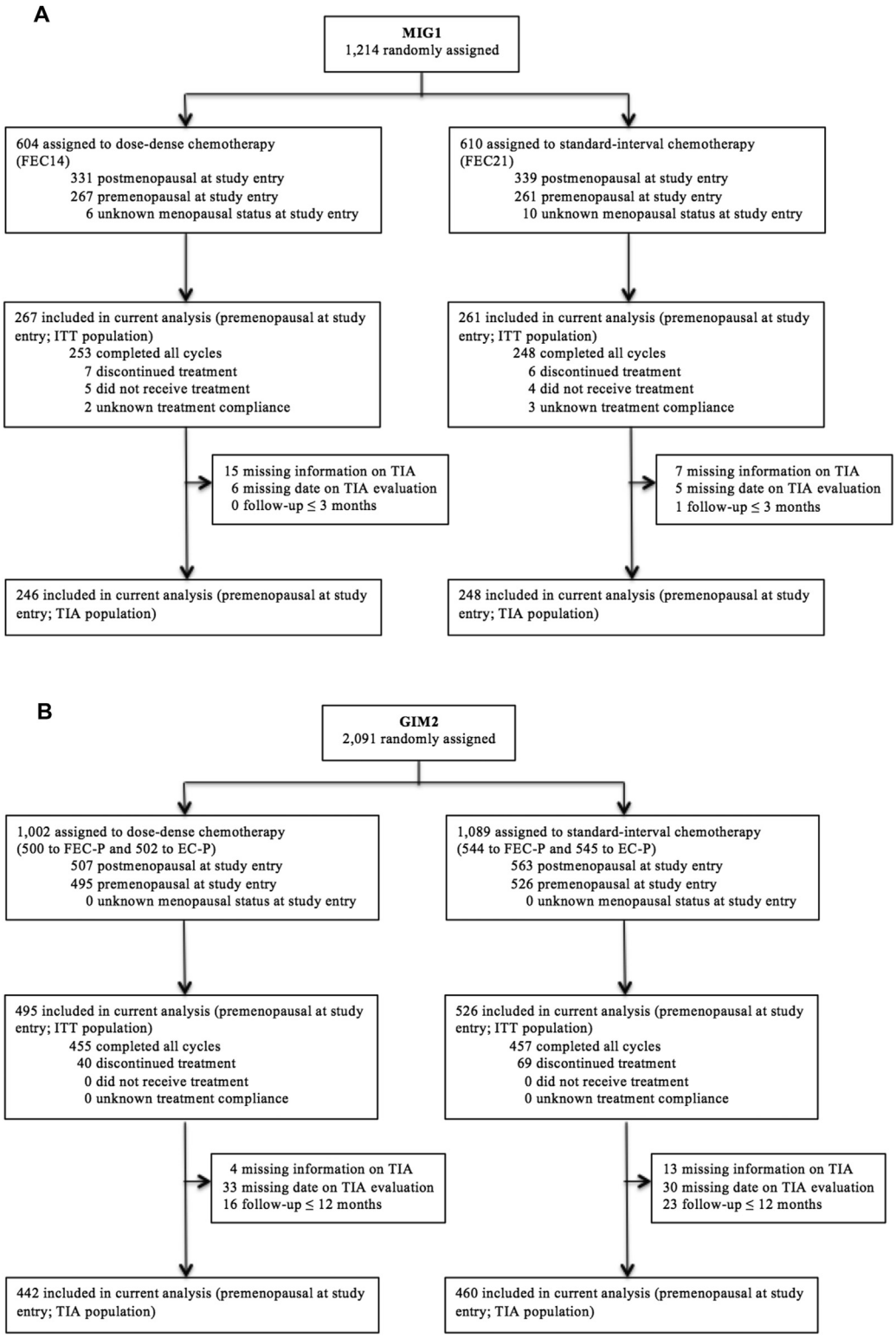

Fig. 1. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the MIG1 (A) and GIM2 (B) studies. Abbreviations: ITT, intention-to-treat; TIA, treatment-induced amenorrhoea; FEC, fluorouracil, epirubicin, cyclophosphamide; EC, epirubicin, cyclophosphamide; P, paclitaxel.

significant improvement in OS as compared with standard-interval chemotherapy (HR, 0.71; p = 0.021) with no increased risk of treatment-induced amenorrhoea (OR, 1.00; p = 0.989).

In the era of personalised medicine, chemotherapy remains a mainstay adjuvant treatment for a large number of breast cancer patients [2]. Dose-dense chemotherapy significantly improves OS as compared

Table 1
Patients' baseline characteristics.

	MIG1		p Value[a]	GIM2		p Value[a]
	Standard-interval CT (No. = 261) No. (%)	Dose-dense CT (No. = 267) No. (%)		Standard-interval CT (No. = 526) No. (%)	Dose-dense CT (No. = 495) No. (%)	
Age at study entry						
>45 years	131 (50.2)	116 (43.4)	0.300	195 (37.1)	191 (38.6)	0.753
40–45 years	62 (23.8)	71 (26.6)		157 (29.9)	151 (30.5)	
<40 years	68 (26.0)	80 (30)		174 (33.1)	153 (30.9)	
Type of surgery						
Mastectomy	108 (41.4)	113 (42.3)	0.860	229 (43.5)	211 (42.6)	0.800
Lumpectomy	152 (58.2)	152 (56.9)		297 (56.5)	284 (57.4)	
Unknown	1 (0.4)	2 (0.7)		0 (0.0)	0 (0.0)	
Tumour size						
pT1	135 (51.7)	141 (52.8)	0.443	257 (48.9)	253 (51.1)	0.428
pT2	106 (40.6)	114 (42.7)		222 (42.2)	206 (41.6)	
pT3–pT4	16 (6.1)	10 (3.8)		46 (8.7)	33 (6.7)	
Unknown	4 (1.5)	2 (0.7)		1 (0.2)	3 (0.6)	
Nodal status						
pN0 (0)	93 (35.6)	94 (35.2)	0.213	0 (0.0)	0 (0.0)	0.752
pN1 (1–3)	104 (39.8)	122 (45.7)		326 (62.0)	310 (62.6)	
pN2 (4–9)	63 (24.1)	49 (18.4)		127 (24.1)	124 (25.1)	
pN3 (≥10)	0 (0.0)	0 (0.0)		73 (13.9)	61 (12.3)	
Unknown	1 (0.4)	2 (0.7)		0 (0.0)	0 (0.0)	
Tumour grade						
G1	16 (6.1)	15 (5.6)	0.207	27 (5.1)	30 (6.1)	0.255
G2	118 (45.2)	140 (52.4)		228 (43.3)	234 (47.3)	
G3	94 (36.0)	79 (29.6)		270 (51.3)	228 (46.1)	
Unknown	33 (12.6)	33 (12.4)		1 (0.2)	3 (0.6)	
HR status						
ER- and/or PR-positive	150 (57.5)	158 (59.2)	0.643	425 (80.8)	401 (81.0)	1.00
ER- and PR-negative	95 (36.4)	91 (34.1)		86 (16.3)	80 (16.2)	
Unknown	16 (6.1)	18 (6.7)		15 (2.9)	14 (2.8)	
HER2 status						
HER-positive	20 (7.7)	24 (9.0)	0.871	119 (22.6)	118 (23.8)	0.359
HER-negative	118 (45.2)	131 (49.1)		334 (63.5)	286 (57.8)	
Unknown	123 (47.1)	112 (41.9)		73 (13.9)	91 (18.4)	

Abbreviations: CT, chemotherapy; pT, pathologic tumour stage; pN, pathologic nodal stage; G, tumour grade; HR, hormone receptors; ER, oestrogen receptor; PR, progesterone receptor.
[a] Fisher exact test excluding unknown data.

to standard-interval chemotherapy [7,8]. Currently, treatment guidelines vary between Europe (where there are no clear recommendations) [18] and the United States (where dose-dense chemotherapy is considered one of the preferred adjuvant regimen for patients with high risk early-stage breast cancer) [19]. To date, for young women requiring adjuvant chemotherapy, there is no evidence to recommend a specific chemotherapy regimen [2]. Our results showed a significant 29% relative improvement in OS for premenopausal women treated with dose-dense chemotherapy as compared with those treated with standard-interval chemotherapy. Of note, a different chemotherapy regimen was used in the two trials (6 cycles of anthracycline-based chemotherapy in the MIG1 study [11] and 4 cycles of anthracycline-based chemotherapy followed by 4 cycles of taxanes in the GIM2 study [12]). Considering the incremental benefit with the addition of taxanes to anthracycline-based regimens [20], and the cumulative dose-related cardiotoxicity of anthracyclines [21], a sequential regimen as in the GIM2 study (which included taxanes and fewer cycles of anthracyclines) should be considered the preferred treatment option.

Prior evidence suggested that the benefit of dose-dense chemotherapy appeared largely driven by effect in hormone receptor-negative tumours [7,8]. Although the efficacy of dose-dense chemotherapy was larger in women with hormone receptor-negative tumours (35% relative gain), our study showed a benefit also in patients with hormone receptor-positive tumours (22% relative gain). This finding might be explained by the notion that premenopausal patients are known to be more sensitive to chemotherapy [22,23]. Young age is an independent factor associated with higher risk of relapse and death [24]; premenopausal patients are more likely to develop aggressive breast cancer subtypes [25]. Hence, premenopausal patients might represent the best candidates for dose-dense chemotherapy.

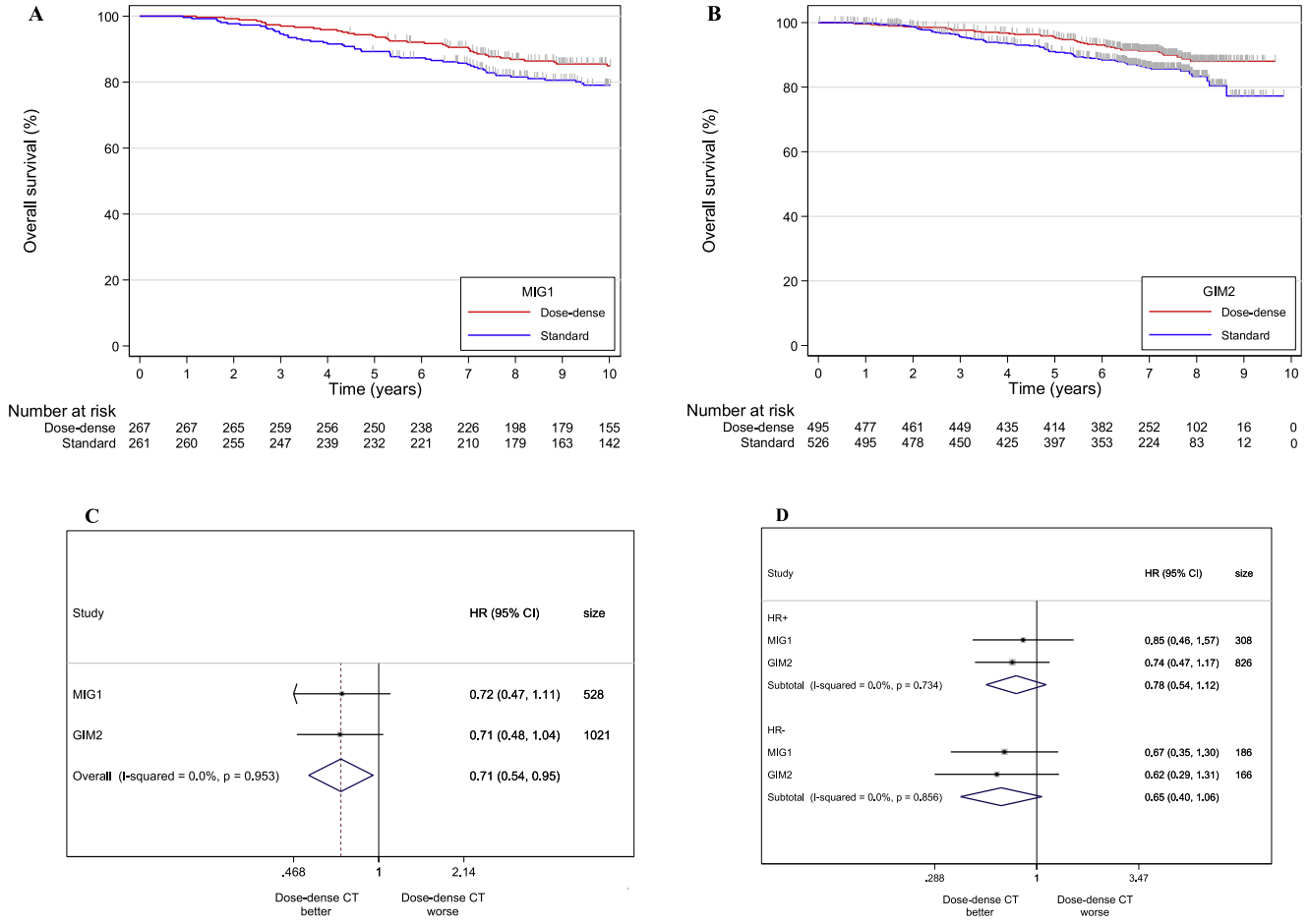

Fig. 2. Overall survival in premenopausal women for the comparison between dose-dense and standard-interval chemotherapy: MIG1 study (A); GIM2 study (B); meta-analysis MIG1 and GIM2 studies (C); meta-analysis stratified by hormone receptor status (D). Abbreviations: HR, hazard ratio; CI, confidence intervals; CT, chemotherapy; HR+, hormone receptor-positive; HR−, hormone receptor-negative.

Moreover, dose-dense schedule might be more socially convenient for young patients, who are generally employed at the time of breast cancer diagnosis. Chemotherapy has been reported to be associated with negative work outcomes in young women with breast cancer leading to prolonged absenteeism [26]. With the use of dose-dense schedule, the overall duration of treatment as well as the recovery from its side-effects (including alopecia) would be decreased as compared to standard-interval chemotherapy, with subsequent possible advantages on the return-to-work process.

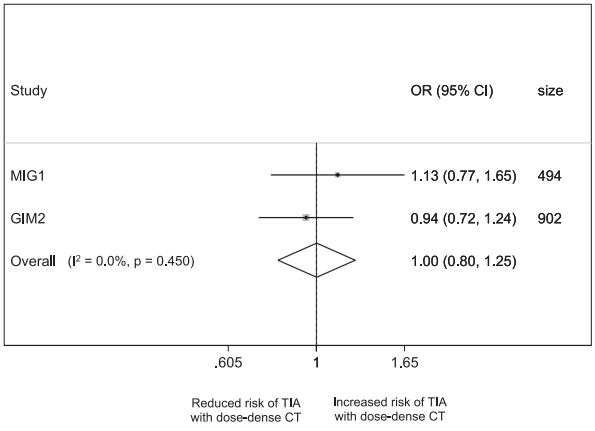

Fig. 3. Treatment-induced amenorrhoea in premenopausal women for the comparison between dose-dense and standard-interval chemotherapy. Abbreviations: OR, odds ratio; CI, confidence intervals; TIA, treatment-induced amenorrhoea; CT, chemotherapy.

In premenopausal patients, a possible negative side-effect of chemotherapy is the occurrence of treatment-induced amenorrhoea and infertility [4]. The most commonly employed anthracycline-based or anthracycline- and taxane-based chemotherapy regimens in breast cancer are associated with an intermediate risk (i.e. 40–60%) of treatment-induced amenorrhoea [4]. Our study confirms the intermediate risk of treatment-induced amenorrhoea with the use of these regimens. Despite a lower cumulative dose of chemotherapy and less cycles, more patients (56%) developed treatment-induced amenorrhoea in the MIG1 study than in the GIM2 study (43%). However, treatment-induced amenorrhoea was evaluated earlier after the end of chemotherapy in the MIG1 study (3 months) than in the GIM2

study (12 months). Although long-term recovery of ovarian function can occur, most of the patients who remain premenopausal resume their menstrual function steadily during the first year after the end of chemotherapy [27]. As previously reported by two small retrospective studies [9,10], our pooled analysis confirmed no increased risk of treatment-induced amenorrhoea with dose-dense chemotherapy, thus suggesting that the greater efficacy of dose-dense chemotherapy seems not to be mediated by a greater activity in suppressing ovarian function.

Some limitations of the present analysis should be considered in the interpretation of the study findings. The MIG1 and GIM2 trials were performed in different eras; hence, the studies differ for median follow-up time, types of adjuvant treatment administered and treatment duration. Furthermore, the occurrence of treatment-induced amenorrhoea was evaluated at a different time-point in the two studies. Despite these limitations, to our knowledge, this is the first planned effort aiming to investigate the optimal chemotherapy regimen in the specific subgroup of premenopausal women with breast cancer. These findings add new potential insight for counselling young patients regarding the choice among the available adjuvant chemotherapy regimens.

In conclusion, dose-dense adjuvant chemotherapy is associated with a significant survival improvement as compared with standard-interval chemotherapy in high-risk, premenopausal breast cancer patients with no increased risk of treatment-induced amenorrhoea. Dose-dense adjuvant chemotherapy, specifically anthracycline- and taxane-based regimens, may be considered the preferred treatment option and should be proposed to all high-risk premenopausal breast cancer patients who are candidates to chemotherapy.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.10.030.

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