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Original Research

Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls

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KEYWORDS
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Abstract ***Background:*** A diagnosis of breast cancer during pregnancy (PrBC) does not impact prognosis if standard treatment is offered. However, caution is warranted as gestational changes in pharmacokinetics may lead to reduced chemotherapy concentration.
Methods: Survival of PrBC patients treated with chemotherapy during pregnancy was compared to non-pregnant breast cancer patients treated with chemotherapy, diagnosed after 2000, excluding patients older than 45 years or with a postpartum diagnosis. The data was registered in two multicenter registries (the International Network of Cancer, Infertility and Pregnancy and the German Breast Group). Cox proportional hazards regression was used to compare disease-free (DFS) and overall survival (OS) between both groups, adjusting for age, stage, grade, hormone receptor status, human epidermal growth factor 2 status and histology, weighted by propensity scoring to account for the differences in baseline characteristics between pregnant patients and controls.
Results: In total, 662 pregnant and 2081 non-pregnant patients were selected. Pregnant patients were more likely to have stage II breast cancer (60.1% vs 56.1%, $p = 0.035$), grade 3 tumors (74.0% vs 62.2%, $p < 0.001$), hormone receptor-negative tumors (48.4% vs 34.0%, $p < 0.001$) or triple-negative breast cancer (38.9% vs 26.9%, $p < 0.001$). Median follow-up was 66 months. In multivariable analysis, DFS and OS were comparable for pregnant and non-pregnant patients (DFS: HR 1.02, 95% CI 0.82–1.27, $p = 0.83$; OS: HR 1.08, 95% CI 0.81–1.45, $p = 0.59$).
Conclusion: Outcome of women with breast cancer treated with chemotherapy during pregnancy is comparable to young non-pregnant women. These results support chemotherapy for PrBC when indicated.

1. Introduction

When studying maternal breast cancer prognosis, breast cancer diagnosed during pregnancy (PrBC) should be distinct from breast cancer diagnosed after delivery (PPBC), which has a more aggressive character with worse prognosis [1]. To date, there is no evidence that PrBC impacts oncological prognosis as long as patients are managed by cancer stage according to standards for non-pregnant patients [2,3]. PrBC has the same characteristics as non-pregnancy related breast cancer in young patients and are thus mainly high grade, triple negative in about one-third and human epidermal growth factor receptor 2 (HER2) positive in one-third [4]. A diagnosis of PrBC often requires consideration of antenatal chemotherapy in order to timely treat and preserve prognosis. Anthracyclines, cyclophosphamide and taxanes can be initiated relatively safe from the second trimester of pregnancy onwards [2]. It is however insufficiently known to what extent gestational physiologic changes, that result in chemodilution, reduce the efficacy of chemotherapy. Indeed, pregnancy is characterized by an increase in plasma volume of up to 34%–70%, which is distributed among the fetus, amniotic fluid, and maternal extra- and intracellular spaces [5]. This increased distribution volume reduces the peak plasma drug concentration [6]. In addition, glomerular infiltration rate (GFR) is increased and hepatic metabolism is altered, including upregulation of enzymes in the cytochrome P450 system, which plays a role in the metabolism of chemotherapeutic agents. Hence, these physiologic gestational changes alter the area under the time–concentration curve, with a potential impact on drug efficacy [5,6]. Recent human data reveal a decrease in chemotherapy exposure in pregnant women, variating from 6.3% (epirubicin) to 24.0% (paclitaxel) of the peak plasma concentration in non-pregnant patients [7].

Because of the fact that clinical trials on PrBC are ethically impossible, most evidence on maternal prognosis comes from multicenter cohort and case control studies, some of them limited by small numbers or lack of detailed information on antenatal treatment [4,8–11]. The German Breast Group (GBG) and the International Network of Cancer, Infertility and Pregnancy (INCIP) previously joined forces to evaluate obstetric and oncologic outcomes of patients diagnosed with PrBC [4,8]. In the previous comparison of 447 PrBC patients with 865 non-pregnant controls, there was no difference in outcome, although the subgroup of patients that received antenatal chemotherapy was too small to draw firm conclusions [4]. The purpose of this larger cohort study is to add evidence, specifically for the group of patients who received chemotherapy antenatally.

2. Material and methods

2.1. Study design

Two multicenter registries with a focus on cancer during pregnancy collaborated in this study; the GBG initiated

registration of PrBC in 2003 whereas INCIP was an European initiative founded in 2014. All registered pregnant patients, diagnosed with stage I–III PrBC between January 1, 2000 and October 31, 2018 who were treated with standard chemotherapy regimens, were included.

For the non-pregnant control group, all stage I–III breast cancer patients younger than 45 years and diagnosed between January 1, 2000 and August 31, 2018 were recruited from the institutional database of the Multidisciplinary Breast Centre (MBC) of the University Hospitals of Leuven and from the non-pregnant cohort of the multicenter GBG registry. From the GBG registry, all patients are younger than 40 years as this is the age limit for recruitment by GBG. Patients with a breast cancer diagnosis within two years after a delivery were excluded for analysis because of the reported inferior survival for postpartum breast cancer cases [1,12].

All patients included were staged and treated according to local hospital policies. Standard chemotherapy regimens included anthracycline-based therapies AC (doxorubicin, cyclophosphamide) and EC (epirubicin, cyclophosphamide), FAC (5-fluorouracil, doxorubicin, cyclophosphamide), FEC (5-fluorouracil, epirubicin, cyclophosphamide) and anthracycline-taxane-based therapies (docetaxel or paclitaxel) +/− carboplatinum. Regimens were administered at standard of care dosages. Non-standard of care regimens included CMF (cyclosphosphamide, methotrexate, fluorouracil), anthracycline monotherapy, and vinorelbine.

Primary outcome was the difference in disease-free survival (DFS) between patients treated with chemotherapy during pregnancy for PrBC and patients not diagnosed during a pregnancy. DFS was defined as time (months) from the date of the first diagnosis until any loco-regional (ipsilateral breast, local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer, any distant recurrence of disease, any secondary malignancy or death due to any cause, whichever occurred first. Patients without events were censored at the date of last contact or at the cut-off date. Secondary outcome was the difference in overall survival (OS) between both groups. OS was defined as the time (months) from the date of first diagnosis to the date of death resulting from any cause. Patients alive were censored at the date of the last contact or at the cut-off date.

The observational multicenter registries were approved by ethics committees [University Hospital Leuven (INCIP) and Goethe Universität Frankfurt, Germany (GBG)] and the studies were registered with ClinicalTrials.gov (INCIP study, NCT00330447; GBG study, NCT00196833).

2.2. Statistical analysis

Prior to the analyses, a power calculation was performed. Based on the previously published cohort and the hypothesis that antenatal chemotherapy is less effective due to gestational physiological changes, a 5-year DFS was assumed to be 71% for control patients and 61% for pregnant patients (HR = 1.443). With 1:1 ratio between pregnant patients and controls, 233 events would be sufficient to have 80% power to the significance level of $\alpha = 0.05$. Adjusting for the 1:3 ratio between pregnant patients and controls and some difference in median follow up between groups, 365 events were considered sufficient.

Since censoring after approximately 14 years seemed to be not completely at random (deaths over-reported compared with last contact with patient alive), an arbitrary cut-off date was defined as the time of the last DFS event in the pregnant group (173 months) + 1 day for survival analyses. Patients with a longer available follow-up were censored.

DFS and OS were compared between pregnant and non-pregnant patients using multivariable Cox proportional hazards regression to adjust for age at diagnosis, stage (I, II, or III), grading (gr 1–2 versus gr 3), histologic tumor type (lobular versus non-lobular), estrogen receptor (ER)/progesterone receptor (PR) status (positive or negative), human epidermal growth factor receptor 2 (HER2) status (HER2-negative versus HER2-positive without or unknown anti-HER2 treatment versus HER2-positive with anti-HER2 treatment) and type of chemotherapy (anthracycline-based only, anthracyclines and taxanes, non-standard treatment). Pregnant patients were allocated to the group treated with anthracyclines and taxanes when at least 15% of the scheduled total dose of taxanes was given during pregnancy. Hazard ratio (HR) with 95% confidence interval (CI) were reported as well as a Wald p-value for each variable in the analysis. Additionally, Kaplan–Meier curves for DFS and OS were created which should be considered purely descriptive.

Given that some baseline characteristics were differently distributed between pregnant women and controls, simply adjusting for those as covariates was not considered sufficient. Instead, an inverse probability weighting by a propensity score based on age, stage, grade, histological tumor type, HR, chemotherapy regimen, HER2 was used for all multivariable analyses [13].

Out of clinical interest, further subgroup analyses for hormone receptor status, stage, age, chemotherapy type and setting (neo-adjuvant versus adjuvant) were performed, and additionally per registry (GBG versus INCIP). In the pregnant group, an exploratory analysis on the number of administrations and the proportion of

Table 1
Clinical characteristics of study group

Characteristic	Overall		Pregnant		Non-pregnant		
	No.	%	No.	%	No.	%	p-value
No. of patients	*2743*		*662*		*2081*		
Year of diagnosis							
Median, range	2012, 2000–2019		2012, 2000–2019		2012, 2000–2019		0.674
Age (years)							
Median, range	37, 19–47		34, 22–47		38, 19–45		<.001
≤30 years	362	13.2	126	19.0	236	11.3	<.001
> 30–35 years	724	26.4	277	41.8	447	21.5	
> 35–40 years	1017	37.1	205	31.0	812	39.0	
> 40 years	640	23.3	54	8.2	586	28.2	
Missing	0		0		0		
Parity							
Median, range	1, 0–10		1, 0–7		1, 0–10		<.001
Nulliparous	715	32.0	225	37.4	490	30.1	<.001
Multiparous	1516	68.0	377	62.6	1139	69.9	
Missing	512		60		452		
Stage							
Stage I	516	19.8	97	16.1	419	20.9	0.035
Stage II	1486	57.0	361	60.1	1125	56.1	
Stage III	603	23.1	143	23.8	460	23.0	
Missing	138		61		77		
Histological tumor type							
Non-lobular	2581	95.2	634	96.9	1947	94.6	0.016
Lobular invasive	131	4.8	20	3.1	111	5.4	
missing	31		8		23		
Grading, dichotomized							
G1-2	928	35.1	159	26.0	769	37.8	<.001
G3	1718	64.9	453	74.0	1265	62.2	
Missing	97		50		47		
HER2 status							
Negative	1937	72.6	443	71.5	1494	73.0	0.472
Positive	730	27.4	177	28.5	553	27.0	
Missing	76		42		34		
Hormone receptor status							
Both ER and PgR negative	1014	37.4	310	48.4	704	34.0	<.001
ER and/or PgR positive	1696	62.6	330	51.6	1366	66.0	
Missing	33		22		11		
Biological subtype							
Luminal A-like (HER2-/HR + grade 1–2)	586	22.2	83	13.7	503	24.8	<.001
Luminal B-like (HER2-/HR + grade 3)	539	20.4	110	18.2	429	21.1	
TNBC	782	29.7	236	38.9	546	26.9	
HER2 positive	730	27.7	177	29.2	553	27.2	
Missing	106		56		50		
Treatment setting							
Neo-adjuvant treatment	1083	39.5	255	38.5	828	39.8	<.001
Adjuvant treatment	1611	58.7	370	55.9	1241	59.6	
Neo-adjuvant and adjuvant treatment	49	1.8	37	5.6	12	0.6	
Missing	0		0		0		
Chemotherapy							
Anthracycline	579	21.1	147	22.2	432	20.8	0.089
Anthracycline + Taxane	1916	69.9	469	70.8	1447	69.5	
Non-standard chemotherapy	248	9.0	46	6.9	202	9.7	
Missing	0		0		0		
Most radical breast surgery							
No breast surgery	8	0.3	4	0.7	4	0.2	0.003
BCS	1295	50.6	262	45.3	1033	52.2	
Mastectomy	1255	49.1	313	54.1	942	47.6	
Missing	185		83		102		
Most radical axilla surgery							
No axilla surgery	47	1.8	12	2.1	35	1.7	0.143
SNB	921	35.4	224	38.6	697	34.5	
ALND	1633	62.8	344	59.3	1289	63.8	
Missing	142		82		60		

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Overall		Pregnant		Non-pregnant		
	No.	%	No.	%	No.	%	p-value
Delay to initiate trastuzumab[a]							
Median, range (in weeks)			17, 1–41				
Trimester of BC diagnosis							
Median, range (in weeks)			17, 0–39				
1st (weeks 1–13)			216	33.3			
2nd (weeks 14–27)			337	52.0			
3rd (> 28 weeks)			95	14.7			
Missing			14				
Initiation chemotherapy during pregnancy							
Median, range (in weeks)			23, 4–39				
< 20 weeks			227	35.4			
20–30 weeks			318	49.6			
> 30 weeks			96	15.0			
Missing			21				
Proportion of cycles chemotherapy during pregnancy (in %)							
Median, range			60.0, 9.1–100				

Abbreviations: BC: breast cancer, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, TNBC: triple negative breast cancer, SNB: node biopsy, ALND: axillar lymph node dissection.

[a] Because not for all cases the date of first administration of trastuzumab was reported, we defined the delay to initiate with trastuzumab as interval between diagnosis and delivery (in weeks).

chemotherapy given during pregnancy was performed to assess whether chemodilution had a plausible effect on maternal outcomes. Cut off of 60% of planned chemotherapy courses during pregnancy was arbitrary chosen based on the median proportion of antenatal chemotherapy in this series.

Clinical variables were reported descriptively (including number of missing values) for cases and controls and compared (if applicable for both groups) between cases and controls using exact test of Fisher (for binary variables), χ2-test (for categorical variables with more than 2 levels) or Wilcoxon test (for continuous variables). All reported *p*-values are two-sided and $p \leq 0.05$ was considered statistically significant and CI symmetrically span 95%. No adjustment for multiple comparisons was planned or performed for the subgroup analyses. All analyses were performed using the SAS statistical software package (version 9.4; SAS Institute, Cary, NC). Missing values of covariates were imputed once, using the method of chained equations making use of IVEware, in order not to lose power due to the missing values [14].

3. Results

In total, 662 pregnant women treated with chemotherapy were recruited from GBG (n = 280) and INCIP (n = 382) for analysis. Survival was compared with 2081 non-pregnant breast cancer patients (GBG n = 885; MBC n = 1196). Clinical characteristics are depicted in Table 1. Pregnant patients were more likely to have stage II breast cancer, grade 3 tumors, ER/PR negative tumors or triple-negative breast cancer.

3.1. Treatment

Most pregnant women were diagnosed in the second trimester of pregnancy. In 44.1% of pregnant patients chemotherapy was initiated in a neo-adjuvant setting, compared to 40.4% in the non-pregnant group ($p < 0.001$). Patients that received neo-adjuvant chemotherapy were diagnosed later in pregnancy and received a lower proportion of total chemotherapy during pregnancy compared to pregnant patients that received chemotherapy in the adjuvant setting (median 23 weeks versus 13 weeks, $p < 0.001$ and 50% versus 75%, $p < 0.001$, for pregnant and controls, respectively). Pregnant patients received neo-adjuvant chemotherapy earlier following diagnosis compared to non-pregnant patients (median 15 days (range 0–134) versus 25 (0–177), $p < 0.001$), whereas in adjuvant setting there was no difference in treatment delay between pregnant and non-pregnant patients (supplementary Tables 1 and 2).

3.2. Survival

With a median follow-up of 66.3 months (51 months for pregnant women and 71 months for non-pregnant women), 87 (13.1%) pregnant women and 274 (13.2%) non-pregnant controls died (Supplementary Figure 1). For pregnant patients, the observed 3- and 5-year DFS and OS was 78.0%, 73.2% and 90.3%, 84.2%, respectively. For non-pregnant patients the observed 3- and 5-year DFS and OS was 85.0%, 78.1% and 94.3%, 89.2%, respectively. Multivariable cox proportional hazard regression for DFS and OS, adjusted for age, stage, grading, histology, hormone receptor status, HER2

Table 2
Multivariable Cox proportional hazard regression.

No. pregnant	No. non-pregnant	Outcome	HR	95% CI	p-value
A. Total study group					
662	2081	DFS	1.024[a]	0.824–1.273	0.830
		OS	1.082[a]	0.810–1.446	0.592
B. Pregnant patients treated with more than 60% of chemotherapy during pregnancy versus controls					
339	2081	DFS	0.811[b]	0.618–1.064	0.130
		OS	0.848[b]	0.584–1.231	0.387
C. Pregnant group, for number of cycles given during pregnancy					
654		DFS	0.941[c]	0.856–1.034	0.203
		OS	0.926[c]	0.817–1.049	0.228
D. Pregnant group, by proportion of chemotherapy during pregnancy					
645		DFS	0.956[d]	0.896–1.020	0.176
		OS	0.969[d]	0.889–1.057	0.479

Multivariable cox proportional hazard regression for DFS and OS, adjusted for age, stage, grading, histology, hormone receptor status, HER2 status and type of chemotherapy.
*Distant disease-free survival (DDFS) was calculated from diagnosis to distant relapse or death.
[a] HR for pregnant versus control.
[b] HR for pregnant patients who received at least 60% of chemotherapy during pregnancy versus control.
[c] HR per 1 cycle increment.
[d] HR per 10% increment.

status and type of chemotherapy, did not reveal a worse prognosis for pregnant patients compared to non-pregnant patients (HR 1.024 (0.824–1.273 $p = 0.830$ for DFS and HR 1.082 (0.810–1.446), $p = 0.592$ for OS) (Table 2). Multivariable analysis in the pregnant group revealed that the number of cycles or proportion of chemotherapy did not impact DFS or OS. Survival of pregnant patients that received more than 60% of the chemotherapy during pregnancy was similar to non-pregnant women. Further subgroup analysis did show comparable results per registry (GBG versus INCIP), hormone-receptor status, molecular subtype, stage, age ($\leq$ 30 years) and chemotherapy (standard versus non-standard treatment) for both DFS and OS (Fig. 1). However, for luminal A breast cancer, pregnant patients had worse OS compared with non-pregnant, whereas DFS was comparable.

4. Discussion

To date, this is the largest cohort comparing DFS and OS of women receiving chemotherapy for PrBC and non-pregnant young breast cancer patients. Survival of PrBC in general was comparable to controls, hereby emphasizing the results of our previous cohort that did not further explore the subgroup with antenatal chemotherapy [4]. In particular, we observed similar outcomes for women who received the majority ($>$ 60%) of chemotherapy during pregnancy compared to non-pregnant controls. Although the impact of gestational physiologic changes on the efficacy of chemotherapy is plausible and a concern, this is not reflected in this cohort. Hence, these results confirm current recommendations to treat pregnant patients as their non-pregnant counterparts, according to standard guidelines with gestation-related treatment adaptations [2].

Recently, we have shown that for chemotherapeutic agents commonly used in breast cancer (doxorubicin, epirubicin, paclitaxel, and docetaxel), decreased drug exposures were observed in pregnant patients [7]. Interestingly, an important inter-drug variation was observed. While pregnancy advances, albumin concentrations decrease and hepatic cytochrome p450 enzymes involved in the taxane metabolism increase, resulting in significant changes most importantly in taxane pharmacokinetics [6]. Indeed the gestation-related changes on chemotherapy concentrations appear to be more important for the highly protein bound taxanes, compared to anthracyclines, resulting in a 24.0% lower peak plasma concentration and 12% lower AUC_{0-48h} for paclitaxel when compared to non-pregnant patients [6,7]. However, in our series, multivariable cox regression analysis did not reveal a negative prognostic effect of the use of taxanes. Since only a subgroup of the present cohort received taxanes, it is prudent to start whenever possible with anthracycline-based treatment during pregnancy, followed by taxanes (as in over 90% of pregnant patients in this series),. [15]. Our results support the recommendation to dose chemotherapy based on the actual body weight of pregnant patients and there is no need to increase the dosage because of pregnancy [2,6,7]. The latter would likely raise maternal and fetal toxicity and risks, including fetal growth restriction and preterm delivery [16].

When antenatal breast cancer treatment is considered, both short-and long-term concerns for the mother and the child-to-be are balanced. With close maternal–fetal surveillance following chemotherapy exposure, fetal and pediatric outcome after antenatal exposure to chemotherapy are reassuring, although a

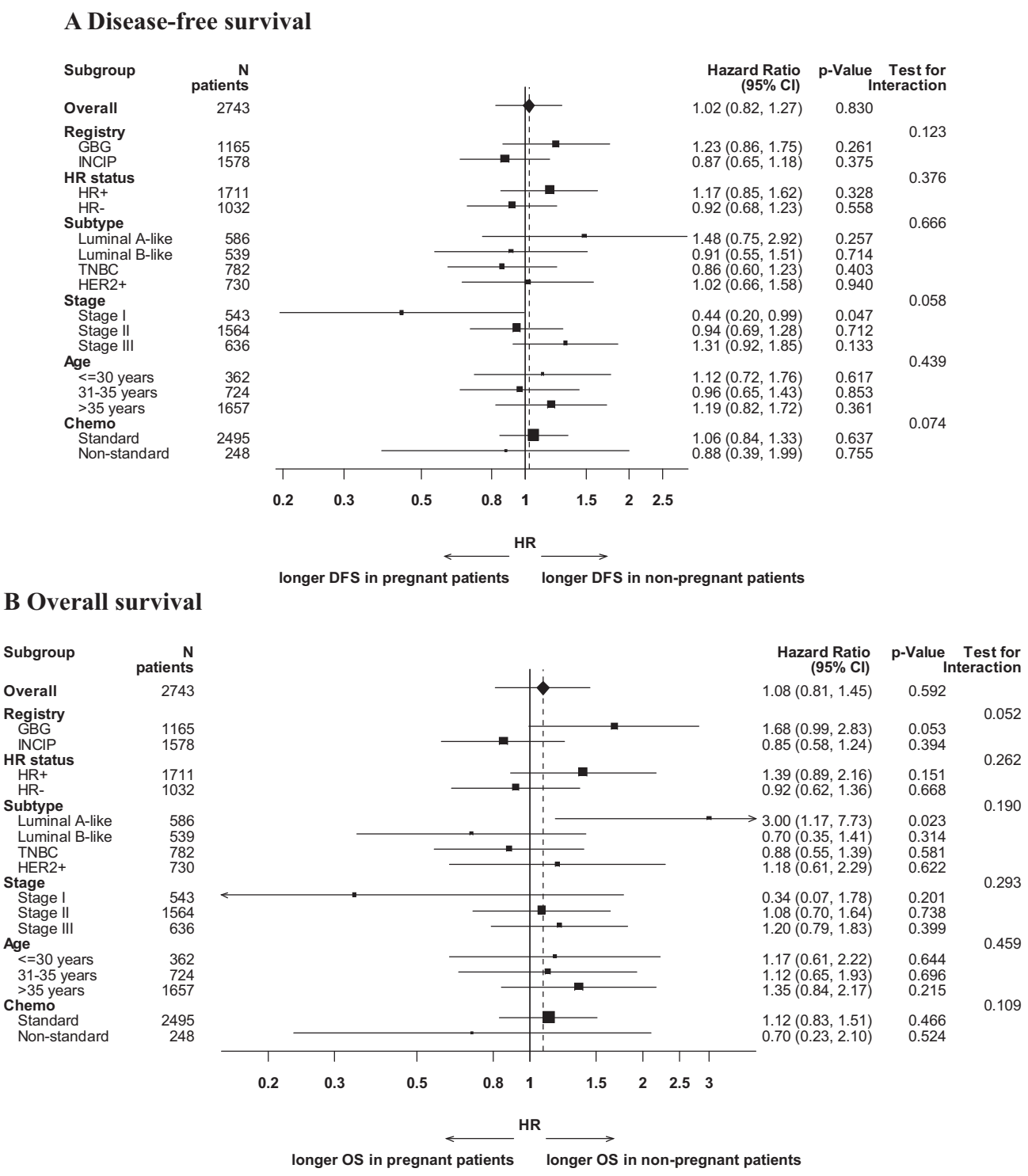

Fig. 1. Forest plots with results of multivariate Cox regression analysis of disease-free survival (DFS) (a) and overall survival (OS) (b) by subgroups of interests (registry, HR (hormone receptor) status, molecular subtype, stage of breast cancer, age at diagnosis, chemotherapy regimen as part of primary treatment (standard vs non-standard).

continuous follow-up of these children remains warranted [17,18]. The data we report now add to maternal safety. It is tempting to speculate that this finding can be extrapolated to other less frequent cancers. In a recent matched case control study including 124 pregnant patients with Hodgkin lymphoma, maternal outcome was also reassuring [19].

As trastuzumab has the ability to cross the placenta and interferes with fetal renal function resulting in oligohydramnios and secondary lung dysplasia, its

antenatal use should be avoided [20]. Trastuzumab treatment delay until after delivery appears not to impact survival in this series (data not shown). As the sequential use of trastuzumab following chemotherapy is a clinically used alternative in non-pregnant breast cancer patients (eg. HERA (HERceptin Adjuvant) trial), the initiation of trastuzumab after delivery in PrBC can be justified in order not to put the fetus at risk [21–23].

In contrast to our previous results, this larger cohort suggests a worse OS for pregnant women receiving chemotherapy for luminal A breast cancer compared to non-pregnant luminal A breast cancer controls. For the other breast cancer subtypes (including luminal B) our data reveal a similar survival for pregnant and non-pregnant women. However, focusing on subgroups further complicates data interpretation. The complex gestation-related hormonal interactions and associations with cancer development and progression are still incompletely understood [24]. Whether there exists a clinical genuine adverse effect of the high gestational estrogen levels on a hormone receptor positive tumor, as suggested in preclinical research, needs further research, with more detailed data including longer follow-up and pathological response following neo-adjuvant chemotherapy [25].

Studying the prognosis of PrBC is challenging because of its rarity, the different diagnostic and treatment approaches within this international setting, as well as the multiple confounders and the large number of patients needed to achieve sufficient power. Although this study is the largest reporting on survival of patients receiving chemotherapy for PrBC, there are several limitations to consider. As 180 pregnant patients and 865 non-pregnant patients were also included in our previously published series, this cohort study is not an independent validation of our results [4]. A major limitation is the partial retrospective data collection, inevitably resulting in missing data; Available follow-up data of non-pregnant controls was 20 months longer compared to pregnant women. The retrospective design in an international collaboration results in a very heterogeneous selected population, staged and treated according to standard local policies. Furthermore, supplementary analyses of particular subgroups of interest are still underpowered. Data were not detailed regarding effective chemotherapy dosages; however, we may assume that chemotherapy in this cohort was prescribed based on actual body weight, as participating centers are following current recommendations. A possible pregnancy-related delay to initiate hormonal treatment was not taken into account in this analysis, however most patients were diagnosed in the second half of pregnancy and were still receiving chemotherapy or surgery after delivery. Furthermore, data were too scarce to explore effects of double HER2 blockade or BMI or prognosis of subgroups according to histological subtype or treatment setting.

5. Conclusions

Prognosis of pregnant patients treated with chemotherapy is comparable to non-pregnant patients. Although gestational-induced alterations in chemotherapy concentrations are likely, these do not seem to affect maternal oncological safety. These results support initiation of standard chemotherapy for PrBC where indicated for oncological reasons at the same dosage as in non-pregnant patients.

Author contributions

Frédéric Amant (FA): conceptualisation, data curation, funding acquisition, investigation, methodology, resources, supervision, validation, writing-original draft and writing-review & editing. Valentina Nekljudova (VN): data curation, formal analysis, investigation, methodology, project administration, software, validation, visualisation, writing-original draft and writing-review & editing. Charlotte Maggen (CM): data curation, investigation, methodology, project administration, software, validation, visualisation, writing-original draft and writing-review & editing. Fenja Seither (FS): data curation, investigation, project administration, software, validation, visualisation, writing-review & editing. Patrick Neven (PN): data curation, investigation, writing-review & editing. Elyce Cardonick (EC): data curation, investigation, writing-review & editing. Sabine Schmatloch (SSc): data curation, investigation, writing-review & editing. Kristel Van Calsteren (KVC): data curation, funding acquisition, investigation, writing-review & editing. Tatjana Cordes (TC): data curation, investigation, writing-review & editing. Jorine de Haan (JDH): data curation, investigation, writing-review & editing. Christianne A.R. Lok (CARL): data curation, investigation, writing-review & editing. Felix Flock (FF): data curation, investigation, writing-review & editing. Ingrid A. Boere (IAB): data curation, investigation, writing-review & editing. Mina Mhallem Gziri (MMG): data curation, investigation, writing-review & editing. Christine Solbach (CS): data curation, investigation, writing-review & editing. Hanne Lefrère (HL): data curation, investigation, writing-review & editing. Andreas Schneeweiss (AS): data curation, investigation, writing-review & editing. Isabell Witzel (IW): data curation, investigation, writing-review & editing. Sabine Seiler (SSe): data curation, investigation, methodology, project administration, software, validation, visualisation, writing-original draft and writing-review & editing. Sibylle Loibl (SL): conceptualisation, data curation, funding acquisition, investigation, methodology, resources, supervision, validation, writing-original draft and writing-review & editing.

SL, FA, VN, CM and SS designed the study. All authors contributed to data collection. SL, FA, VN, CM, FS and SS gathered and interpreted the data. VN

analysed the data (statistics). VN, SL, FA and CM designed tables and figures. The first draft of the article was written by SL, FA, VN, CM, FS and SS, and all other authors revised the article for the final draft. All authors agreed with the final draft for publication.

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Conflict of interest statement

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Appendix A. Supplementary data

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