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Prognostic role of chemotherapy-induced neutropenia in first-line treatment of advanced ovarian cancer. A pooled analysis of MITO2 and MITO7 trials

Gennaro Daniele [a], Laura Arenare [a], Giovanni Scambia [b], Carmela Pisano [c], Roberto Sorio [d], Enrico Breda [e], Sabino De Placido [f], Antonella Savarese [g], Gabriella Ferrandina [h,1], Francesco Raspagliesi [i], Pierluigi Benedetti Panici [j], Antonella Ferro [k], Anita Rimanti [l], Gennaro Cormio [m], Domenica Lorusso [b], Sabrina Chiara Cecere [c], Simona Scalone [d], Valentina Angela Marsico [e], Cinzia Cardalesi [f], Francesco Cognetti [g], Vanda Salutari [h], Laura Attademo [c], Lorenzo Guizzaro [n], Clorinda Schettino [a], Maria Carmela Piccirillo [a], Francesco Perrone [a,2], Ciro Gallo [n,2], Sandro Pignata [c,*,2]

[a] Unità Sperimentazioni Cliniche, Istituto Nazionale Tumori - IRCCS- Fondazione G.Pascale, Napoli, Italia
[b] Ginecologia Oncologica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, 00168 Roma, Italy
[c] Oncologia Clinica Sperimentale Uro-Ginecologica, Istituto Nazionale Tumori - IRCCS- Fondazione G.Pascale, Napoli, Italia
[d] Oncologia B, Centro di Riferimento Oncologico, 33081 Aviano, PN, Italy
[e] Oncologia Medica, Ospedale S. Giovanni Calibita Fatebenefratelli, 00186 Roma, Italy
[f] Dipartimento di Medicina Clinica e Chirurgia, Università Federico II, Napoli, Italy
[g] Oncologia Medica 1, IRCCS Istituto Nazionale Tumori Regina Elena, 00144 Roma, Italy
[h] Ginecologia Oncologica, Centro di Ricerca e Formazione ad Alta Tecnologia nelle Scienze Biomediche, Università Cattolica del Sacro Cuore, 86100 Campobasso, Italy
[i] Chirurgia Ginecologica, Istituto Nazionale Tumori, IRCCS, 20133 Milano, Italy
[j] Ginecologia Oncologica, A.O.U. Policlinico Umberto I, 00161 Roma, Italy
[k] Oncologia Medica Ospedale S. Chiara, 38122 Trento, Italy
[l] Oncologia, ASST Mantova, 46100 Mantova, Italy
[m] Ginecologia Oncologica, IRCCS Istituto Oncologico "Giovanni Paolo II", Bari & Department of Biomedical Sciences and Oncology, University "Aldo Moro" Bari, 70124 Bari, Italy
[n] Statistica Medica, Università della Campania Luigi Vanvitelli, 80138 Napoli, Italy

HIGHLIGHTS

- Chemotherapy-induced neutropenia (CIN) has prognostic value in several cancer conditions.
- Previously available data on CIN prognostic value in first line treatment of ovarian cancer are contrasting.
- In two large MITO trials we found no significant prognostic value of CIN.
- Lack of prognostic value of CIN in ovarian cancer was confirmed by meta-analyses with other published results.
- This might derive from the use of AUC rather than BSA for dosing carboplatin, a key drug in this setting.

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ABSTRACT

Background. Chemotherapy-induced neutropenia (CIN) has been associated with improved prognosis in several cancer conditions. Contrasting data have been produced in ovarian cancer.

* Corresponding author at: Oncologia Clinica Sperimentale Uro-Ginecologica, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS Fondazione Pascale, via Mariano Semmola, 80131 Napoli, Italy.
E-mail addresses: g.daniele@istitutotumori.na.it (G. Daniele), l.arenare@istitutotumori.na.it (L. Arenare), giovanni.scambia@policlinicogemelli.it (G. Scambia), c.pisano@istitutotumori.na.it (C. Pisano), rsorio@cro.it (R. Sorio), deplacid@unina.it (S. De Placido), antonella.savarese@ifo.gov.it (A. Savarese), francesco.Raspagliesi@istitutotumori.mi.it (F. Raspagliesi), pierluigi.benedettipanici@uniroma1.it (P.B. Panici), antonella.ferro@apss.tn.it (A. Ferro), anita.rimanti@asst-mantova.it (A. Rimanti), gennaro.cormio@uniba.it (G. Cormio), s.cecere@istitutotumori.na.it (S.C. Cecere), sscalone@cro.it (S. Scalone), cinzia.cardalesi@unina.it (C. Cardalesi), francesco.cognetti@ifo.gov.it (F. Cognetti), c.schettino@istitutotumori.na.it (C. Schettino), m.piccirillo@istitutotumori.na.it (M.C. Piccirillo), f.perrone@istitutotumori.na.it (F. Perrone), ciro.gallo@unicampania.it (C. Gallo), s.pignata@istitutotumori.na.it (S. Pignata).
[1] Present address: Fondazione Policlinico Universitario A. Gemelli, IRCCS, Universita' Cattolica, Roma, Italy.
[2] These authors contributed equally.

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Patients and methods

A retrospective-prospective analysis was performed to test prognostic value of severe (grades 3–4) or any grade (grade ≥ 1) CIN during first-line carboplatin-based treatment of advanced ovarian cancer patients enrolled in the MITO-2 and MITO-7 randomized phase 3 trials. Patients who had received chemotherapy were eligible if toxicity data were not missing. Progression-free (PFS) and overall survival (OS) were the end-points. To avoid the time-dependent bias, a landmark at 18 weeks from randomization was applied. Multivariable Cox model was applied for statistical analyses. Three random-effect meta-analyses were also conducted pooling MITO data with other published studies.

Results

Overall, 1603 out of 1630 enrolled patients were eligible. Severe CIN was reported in 734 (45.8%) patients and any grade CIN in 1176 (73.4%). After landmark application, 1493 (with 901 events) and 1548 (with 462 events) patients were included in PFS and OS analysis, respectively. Neither severe (PFS hazard ratio [HR] = 0.90, 95%CI: 0.78–1.03, $P = 0.13$; OS HR = 0.97, 95%CI: 0.80–1.18, $P = 0.79$) nor any grade CIN (PFS HR = 0.92, 95%CI: 0.78–1.09, $P = 0.34$; OS HR = 1.12, 95%CI: 0.90–1.42, $P = 0.33$) were significantly predictive of prognosis. Meta-analyses with other published data confirmed no prognostic value of severe and any grade CIN.

Conclusion

The present analysis of two large MITO trials, combined with other available evidence, shows that CIN (severe or any grade) has no significant prognostic role for advanced ovarian cancer patients receiving first-line carboplatin-based chemotherapy.

1. Introduction

Chemotherapy-induced neutropenia (CIN) has been associated with longer survival in several cancer conditions [1–5]. The mechanistic hypothesis underlying this effect is that CIN could represent a biomarker of effective dosing of anticancer drugs.

Contrasting data have been produced in ovarian cancer, where chemotherapy with carboplatin and paclitaxel remains the backbone treatment for the large majority of patients, even in the era of antiangiogenetic and target-based drugs [6–10]. Among three studies performed in first-line treatment, two found a prognostic value of CIN in ovarian cancer [6,10]. Carus et al. reported that any grade neutropenia was associated with longer overall survival (56 months median survival compared to 23 months median survival of those without neutropenia) in a series of 118 ovarian cancer patients receiving carboplatin-based chemotherapy [6]. Tewari et al., in a post-hoc exploratory analysis of the Gynecologic Oncology Group (GOG) protocol 182 found that among 3447 eligible patients those suffering severe (grade 3 or higher) neutropenia had a longer survival with a 0.86 hazard ratio (HR) of death (95% CI 0.74 to 0.99) as compared to those having no or mild neutropenia [10]. On the contrary, in a series of 179 patients receiving carboplatin plus paclitaxel, no prognostic value of severe CIN was found by Kim et al. [7]

Using the data prospectively collected within two large randomized clinical trials performed by the MITO (Multicentre Italian Trials in Ovarian cancer) group, namely the MITO2 and MITO7, we planned a post-hoc pooled analysis to test whether the occurrence of neutropenia during first-line chemotherapy was a significant prognostic factors for ovarian cancer patients.

2. Methods

A retrospective-prospective study design [11] was applied to two phase 3 randomized MITO trials (MITO2 and MITO7), that involved ovarian cancer patients, whose primary analyses have already been published [12,13]. Briefly, MITO2 compared an experimental doublet (carboplatin plus liposomal doxorubicin [PLD]) to the standard carboplatin plus paclitaxel regimen, enrolled 820 patients (from January 2003 to November 2007), and no statistically significant difference was found between the two arms in terms of progression-free survival (PFS), overall survival (OS), response rate and quality of life [12]. MITO7 compared an experimental weekly schedule of carboplatin plus paclitaxel to the standard every 3 weeks schedule of the same drugs, enrolled 810 patients (between November 2008 and March 2012), and no statistically significant difference was found between the two arms in terms of PFS and OS, although quality of life tended to be better with the weekly schedule [13].

The two trials shared many features: both were randomized trials, performed in the same population of advanced ovarian cancer patients undergoing first-line chemotherapy; the same standard arm was present in both studies and the planned treatment duration was the same in both trials; in both trials carboplatin was dosed according to Calvert's formula where creatinine clearance was approximated to eGFR using the Cockroft-Gault formula; neither capping nor adjustment for ideal body weight was planned; management of neutropenia followed the same rules in the two studies, with no use of prophylactic GCSF and 20% dose reduction of all drugs at the next cycle in case of neutrophil count <500/L; methods for toxicity data collection and follow-up rules were very similar in both trials and were managed at the same trial centre (Clinical Trial Unit of the National Cancer Institute of Napoli, Italy); carboplatin was always dosed in terms of AUC while the companion drugs (either paclitaxel or PLD) were dosed as mg/m^2; no significant difference in time-to-event analyses (PFS and OS) was found in either trial.

Neutropenia was codified according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 in MITO2, and the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, in MITO7. However, definition of neutropenia grades does not change between the two scales: grade 1 if absolute neutrophil count [ANC] < 2000/mm^3, grade 2 if ANC < 1500/mm^3, grade 3 if ANC < 1000/mm^3, and grade 4 if ANC < 500/mm^3. For the present study, chemotherapy-induced neutropenia (CIN) was defined as the worst grade of neutropenia suffered by each patient during study treatment. CIN was then defined as severe (grades 3–4) or any grade (grade ≥ 1).

Relative dose intensity of treatment was calculated for each patient by a) dividing the sum of delivered doses over the entire treatment (measured as AUC for carboplatin and as mg/m^2 for paclitaxel and PLD) of each drug by the time from beginning of treatment to the end of the last cycle, b) calculating the ratio between delivered and planned dose intensity for each drug, and c) calculating the mean of the relative

dose-intensity of the two drugs in each doublet; therefore, for each patient a single relative dose-intensity value is reported representing the percentage of planned treatment that was actually delivered over the time.

2.1. Statistical methods

Characteristics of the patient population were described overall and according to CIN grades (0, 1–2, 3–4). The association between categorical variables and CIN grades were tested by Pearson Chi Square; ANOVA was applied for continuous variables. All statistical tests were two tailed and *P* values of <0.05 were considered as significant.

The risk of developing neutropenia typically increases over the time during treatment, and a time-dependent bias may arise, since patients who develop neutropenia must have survived until the moment they developed neutropenia [14]. To counteract this bias, we applied the landmark strategy, where patients censored or having an event before the predefined landmark time were excluded from the analysis. A threshold of 18 weeks from study entry was defined to cover the entire planned treatment period; although theoretically it was possible that some patients could be still on treatment at 18 weeks, because of delays of chemotherapy administration, no patient worsened her CIN category after the landmark time. The same methodology had been applied by Tewari et al. [10]

We used both PFS and OS as study endpoints. PFS was defined as the time from randomization to the date of the first disease progression or death without progression, whichever occurred first. OS was defined as the time from randomization to the date of death. For both endpoints, patients not reaching an event were censored at the date of last information on their vital status.

Two main analyses were performed. The first one evaluated the prognostic role of severe (grades 3–4) CIN vs non severe (grades 0–2) CIN, while the second one assessed the role of any grade CIN (grades 1–4) vs absence of CIN (grade 0).

All statistical analyses were stratified by treatment arm (standard carboplatin plus paclitaxel, carboplatin plus PLD, weekly carboplatin plus paclitaxel), number of cycles of chemotherapy (6, <6) and size of participating centre (according to tertiles of the distribution of centres ordered by the number of enrolled patients).

PFS and OS curves were estimated using the Kaplan–Meier method and compared with a stratified Log Rank test. Stratified multivariable Cox models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI), including age (continuous), body surface area (continuous), ECOG performance status (0–1, 2), stage (I–II, III, IV) and residual disease after initial surgery (none, ≤1 cm, >1 cm, not operated) as other covariates.

Prognostic value of severe and any grade CIN was also described separately in the three treatment arms, in forest plots reporting the HR of PFS and OS derived from multivariable Cox models; first-order interactions between CIN and treatment arm were tested with the likelihood-ratio test of two nested models, with and without interaction.

Finally, to allow interpretation of our findings in the context of other relevant evidence we performed three random effect meta-analyses combining the data of published first-line treatment trials [6,7,10].

Statistical analyses were performed using Stata/MP for Windows (version 14.2).

3. Results

A total of 1630 patients were pooled from the MITO2 (820) and MITO7 (810) trials. Out of them, 1603 patients were eligible for the present study, excluding 16 patients who did never receive chemotherapy and 11 whose toxicity data were missing. Further 110 patients were excluded because they were censored or progressed before 18 week leading to 1493 patients being included in the PFS landmark population. Conversely 1548 patients were included in the OS landmark population, because 55 were censored or died before 18 weeks (Fig. S1 online).

In the whole eligible population, the median age was 58.9 years. Overall, 97.1% of the patients had a performance status of 0–1, 76.9% a FIGO stage I or II, 67.7% a serous histology, and 61.3% had been suboptimally debulked at initial surgery. Moreover, 86.5% of the patients had received the planned number of 6 cycles of treatment and the median relative dose intensity of treatment was 0.85. There were no evident differences in patients' characteristics among the whole eligible, PFS landmark and OS landmark populations, but for number of cycles, as expected. Grades 3–4 neutropenia was reported in 45.8%, 47.5% and 46.9% of the patients in the three study populations, respectively (Table 1).

In the whole patient population CIN occurred more frequently among women treated with carboplatin plus PLD and among those receiving 6 rather than <6 cycles of chemotherapy. A mild inverse association was also found with BSA. Relative dose intensity decreased among patients experiencing neutropenia, as a consequence of dose reductions and treatment delays planned in case of toxicity (Table S1 online). Similar findings were found in the PFS and OS landmark populations (Tables S2 and S3 online).

Overall, 901/1493 patients (60.3%) had a PFS event in the PFS landmark population, with a median PFS of 15.5 months (95% CI: 14.0–17.1) and 462/1548 patients (29.8%) died in the OS landmark population, with a median OS of 57.5 months (95% CI: 46.4–77.8).

Median PFS was 14.7 months versus 15.9 months for patients with CIN grades 0–2 versus those with CIN grades 3–4 (Fig. 1a), and the HR of PFS for the latter group was 0.90 (95% CI: 0.78–1.03), with a *P*-value of 0.13, in the multivariable model (Table 2, left side). Median OS was

Table 1
Patients characteristics in the whole eligible, PFS landmark and OS landmark populations.

	Whole eligible population ($N = 1603$)	PFS landmark population ($N = 1493$)	OS landmark population ($N = 1548$)
Age, median (IQR)	58.9 (50.7–66.6)	58.8 (50.5–66.2)	58.8 (50.6–66.3)
Body surface area, median (IQR)	1.60 (1.52–1.72)	1.60 (1.52–1.72)	1.60 (1.52–1.72)
Performance status, n (%)			
0–1	1556 (97.1%)	1453 (97.3%)	1508 (97.4%)
2	47 (2.9%)	40 (2.7%)	40 (2.6%)
FIGO stage, n (%)			
I–II	1232 (76.9%)	1168 (78.2%)	1202 (77.6%)
III–IV	371 (23.1%)	325 (21.8%)	346 (22.4%)
Histology, n (%)			
Serous	1086 (67.7%)	1020 (68.3%)	1054 (68.1%)
Clear cell/mucinous	111 (6.9%)	95 (6.4%)	103 (6.7%)
Other	366 (22.8%)	348 (23.3%)	357 (23.1%)
Missing	40 (2.5%)	30 (2.0%)	34 (2.2%)
Residual disease, n (%)			
None	621 (38.7%)	605 (40.5%)	613 (39.6%)
≤1 cm	243 (15.2%)	231 (15.5%)	238 (15.4%)
>1 cm	406 (25.3%)	370 (24.8%)	393 (25.4%)
Not operated	333 (20.8%)	287 (19.2%)	304 (19.6%)
Treatment, n (%)			
Carboplatin-paclitaxel	803 (50.1%)	754 (50.5%)	777 (50.2%)
Carboplatin-PLD	400 (25.0%)	368 (24.6%)	389 (25.1%)
Carboplatin-paclitaxel weekly	400 (25.0%)	371 (24.8%)	382 (24.7%)
Chemotherapy cycles, n (%)			
<6	217 (13.5%)	116 (7.8%)	163 (10.5%)
6	1386 (86.5%)	1377 (92.2%)	1385 (89.5%)
Relative dose intensity, median (IQR)	0.85 (0.72–0.94)	0.84 (0.72–0.93)	0.85 (0.72–0.93)
Worst grade of neutropenia, n (%)			
0	427 (26.6)	370 (24.8)	395 (25.5)
1	139 (8.7)	124 (8.31)	133 (8.59)
2	303 (18.9)	290 (19.4)	295 (19.1)
3	483 (30.1)	469 (31.4)	476 (30.8)
4	251 (15.7)	240 (16.1)	249 (16.1)

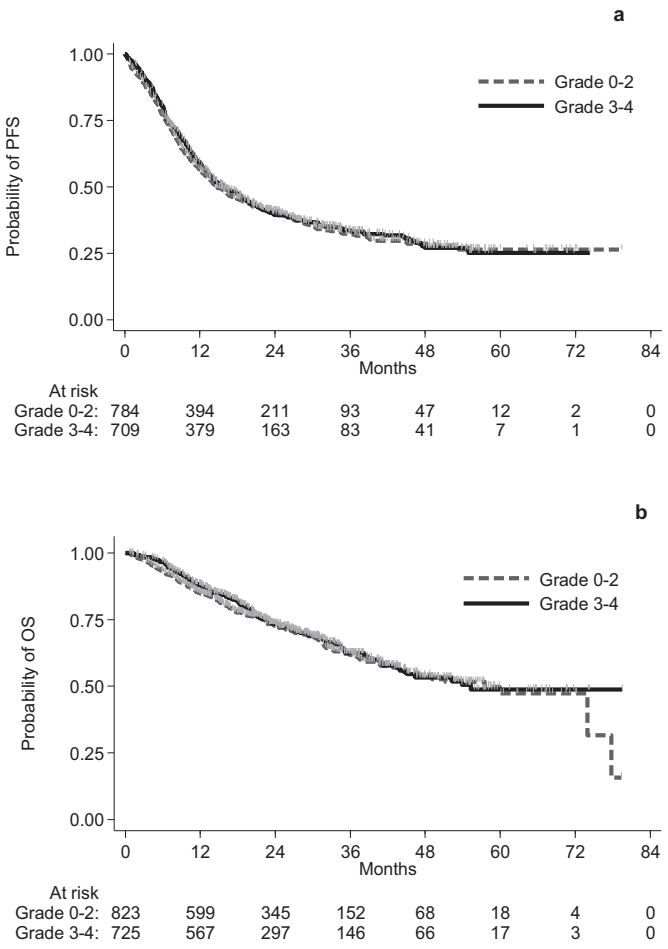

Fig. 1. Progression-free (a) and overall survival (b) Kaplan-Meier curves according to occurrence of severe grade CIN. Vertical lines represent censoring.

57.5 months versus 55.3 months for patients with CIN grades 0–2 versus those with CIN grades 3–4 (Fig. 1b), and the HR of OS for the latter group was 0.97 (95% CI: 0.80–1.18), with a *P*-value of 0.79, in the multivariable model (Table 2, right side).

Table 2
Multivariable analysis* with severe neutropenia.

	PFS (901 events/1493 patients)			OS (462 events/1548 patients)		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Worst grade of neutropenia			0.13			0.79
Grade 0–2	1.00	Reference		1.00	Reference	
Grade 3–4	0.90	(0.78–1.03)		0.97	(0.80–1.18)	
Age (continuous)	1.01	(1.01–1.02)	<0.001	1.01	(1.00–1.02)	0.03
Body surface area (continuous)	0.84	(0.54–1.31)	0.45	0.92	(0.50–1.70)	0.80
Performance status			0.88			0.34
0–1	1.00	Reference		1.00	Reference	
2	1.03	(0.70–1.52)		1.28	(0.77–2.12)	
FIGO stage			<0.001			<0.001
I–II	1.00	Reference		1.00	Reference	
III	2.70	(2.03–3.60)		2.57	(1.58–4.18)	
IV	3.85	(2.81–5.26)		4.26	(2.55–7.10)	
Residual disease			<0.001			<0.001
None	1.00	Reference		1.00	Reference	
≤1 cm	1.96	(1.58–2.44)		1.99	(1.42–2.80)	
>1 cm	2.37	(1.95–2.88)		3.00	(2.21–4.06)	
Not operated	2.82	(2.29–3.48)		3.82	(2.77–5.26)	

* Stratified by size of centre, treatment arm and number of cycles.

Median PFS was 15.2 months versus 15.6 months for patients without CIN (grade 0) versus those with grade ≥ 1 CIN (Fig. 2a), and the HR of PFS for the latter group was 0.92 (95% CI: 0.78–1.09), with a *P*-value of 0.34, in the multivariable model (Table 3, left side). Median OS was 57.5 months versus 74.0 months for patients without CIN (grade 0) versus those with grade ≥ 1 CIN (Fig. 2b), and the HR of OS for the latter group was 1.12 (95% CI: 0.90–1.42) with a *P*-value of 0.33, in the multivariable model (Table 3, right side).

Description of prognostic value of CIN according to treatment arm is reported in Fig. S2 online. There was a significant interaction ($P = 0.046$) in the analysis of severe CIN effect on PFS, where prognostic effect was visible in the group of patients treated with weekly carboplatin plus paclitaxel (the experimental arm of the MITO7 trial) but not in the other treatment arms.

The pooled prognostic effect of severe and any grade CIN, estimated by the random effect meta-analysis model including data available from the other published trials is described in Fig. 3. No one of these meta-analyses produced significant results. With severe CIN, PFS HR was 0.94 (95%CI 0.81–1.08) and OS HR was 0.93 (95% CI 0.80–1.08). For any grade CIN, only OS data were available for pooling and the OS HR was 0.85 (95% CI 0.46–1.58) with a significant heterogeneity between the two pooled studies.

4. Discussion

In this study we did not find a statistically significant prognostic role of having developed CIN on PFS and OS in ovarian cancer women, participating to two large randomized MITO clinical trials, who survived

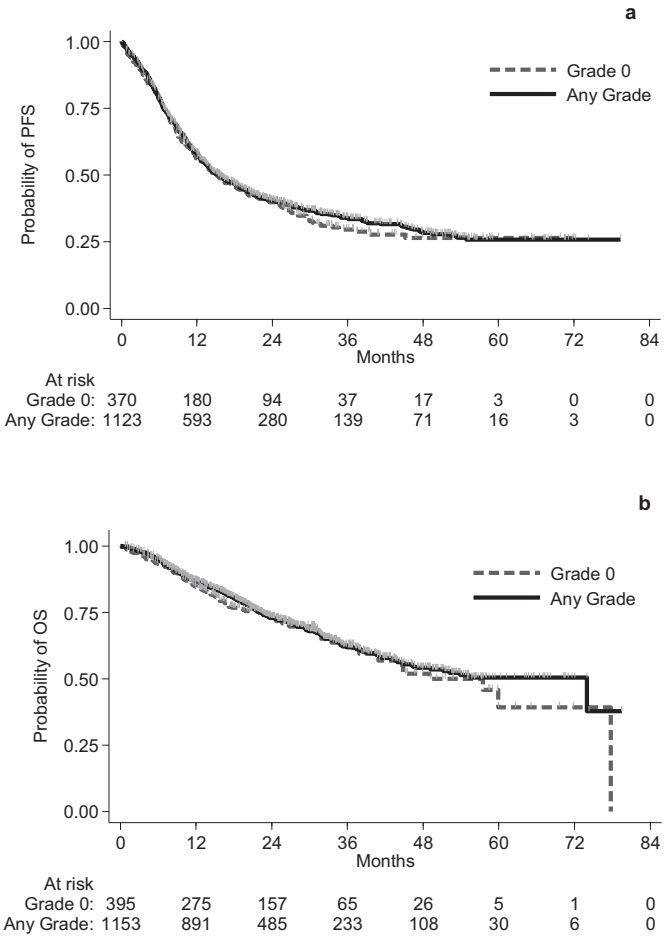

Fig. 2. Progression-free (a) and overall survival (b) Kaplan-Meier curves according to occurrence of any grade CIN. Vertical lines represent censoring.

Table 3
Multivariable analysis* with any grade CIN.

	PFS (901 events/1493 patients)			OS (462 events/1548 patients)		
	HR	(95% CI)	P	HR	(95% CI)	P
Worst grade of neutropenia			0.34			0.33
Grade 0	1.00	Reference		1.00	Reference	
Any grade	0.92	(0.78–1.09)		1.12	(0.90–1.42)	
Age (continuous)	1.01	(1.01–1.02)	<0.001	1.01	(1.00–1.02)	0.03
Body surface area (continuous)	0.84	(0.54–1.31)	0.45	0.95	(0.52–1.76)	0.88
Performance status			0.83			0.36
0–1	1.00	Reference		1.00	Reference	
2	1.04	(0.71–1.54)		1.27	(0.76–2.11)	
FIGO stage			<0.001			<0.001
I–II	1.00	Reference		1.00	Reference	
III	2.68	(2.02–3.57)		2.55	(1.57–4.16)	
IV	3.82	(2.79–5.23)		4.21	(2.53–7.02)	
Residual disease			<0.001			<0.001
None	1.00	Reference		1.00	Reference	
≤1 cm	1.96	(1.58–2.44)		2.00	(1.42–2.81)	
>1 cm	2.37	(1.95–2.88)		3.02	(2.23–4.08)	
Not operated	2.82	(2.28–3.48)		3.86	(2.80–5.32)	

* Stratified by size of centre, treatment arm and number of cycles.

the first 18 weeks of treatment. Results did not change when our data were meta-analysed with findings of other published papers on first-line treatment, leading to no prognostic value of severe or any grade CIN [6,7,10]. Interestingly, even if CIN produced lower dose-intensity due to protocol planned dose reductions, this did not affect the outcome, therefore suggesting that dose-reduction following CIN is safe and does not negatively impact on survival.

Two studies, in subsequent lines of treatment, found a significant prognostic value of chemotherapy induced myelotoxicity. In the Calypso study, dedicated to patients with platinum-sensitive recurrent ovarian cancer, any grade leukopenia after the first cycle was significantly predictive of PFS among patients receiving carboplatin plus paclitaxel, but not among those receiving carboplatin plus PLD. [8] Being aware of heterogeneity of the treatment arms in our analysis, we explored whether any difference in the prognostic value of CIN (either severe or any grade) could be at least partially attributed to a different behaviour in the doublets that were used in our trials. Actually our data do not support any significant interaction between the type of doublet and the prognostic value of CIN. In any case, it should be underlined that there are many differences between the Calypso and the MITO analysis, in terms of line of treatment (second vs first), type of myelotoxicity (leucopenia vs neutropenia) and timing of its evaluation (first cycle only vs the whole 6 cycles treatment course). Finally, in a smaller study including patients with several lines of treatment, severe CIN was predictive of both PFS and OS [9].

The prognostic value of myelosuppression (leukopenia or neutropenia) seems much more relevant in other clinical settings. A meta-analysis published in 2011 pooled 13 studies accounting for 9528 patients receiving first-line or adjuvant/neoadjuvant treatment for several cancer types, breast, NSCLC, Hodgkin, gastric, cervical, esophageal, colorectal and ovarian [4]. The OS HR found for patients with severe leukopenia/neutropenia was 0.69 (95% CI 0.64–0.75) with no significant heterogeneity among the different studies; the result of this meta-analysis did not significantly vary according to the treatment setting (type of cancer and stage of disease), the use of neutropenia or leukopenia as explanatory variable, the statistical methods applied (landmark analysis or not), and the quality of the report. However, this meta-analysis included only one small trial in ovarian cancer [7]. In addition, a prospective trial testing whether the intrapatient dose escalation of carboplatin based on neutrophils and platelets count was more effective than fixed-dose treatment yielded negative results, with no benefit and more toxicity in the experimental arm [15]. Similar negative results were found in a randomized trial in small-cell lung cancer [16].

Among the explanations suggested for the significant prognostic role of CIN in several clinical settings, a simple one is that absence of myelotoxicity is the effect of underdosing in individual patients, producing worse outcome [2,4]. Therefore, lack of prognostic value of CIN in ovarian cancer might be explained by the fact that AUC dosing of carboplatin, the cornerstone of chemotherapy in this disease, prevents underdosing more than dosing strategies based on body surface area (BSA). BSA was introduced as a method to allow extrapolation of dosing from rodents to human in order to define initial dose of phase 1 trials with cytotoxic drugs, at the beginning of the era of chemotherapy; but, thereafter, it became the method commonly used for dosing cytotoxic drugs in clinical practice, even without a solid scientific basis

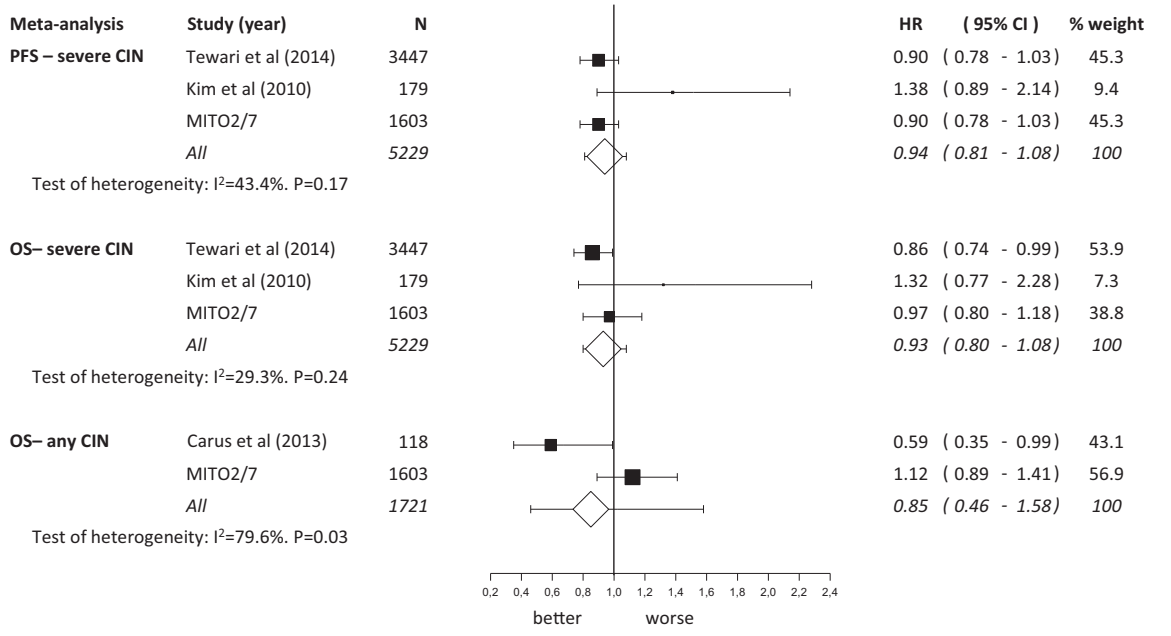

Fig. 3. Prognostic value of severe and any grade CIN in random-effect meta-analyses with other published trials.

[17]. It is recognised, indeed, that BSA is inaccurate because it does not account for drug metabolism and clearance from major organs; hence, it is likely that underdosing occur in a significant proportion of patients in clinical practice, due to the interpatient variability [18]. It is conceivable that in the case of ovarian cancer, where the cornerstone drug is dosed according to AUC, accounting for individual variability in metabolism and clearance, the interpatient variability of drug exposure may be reduced. In addition, underdosing may cause more or less evident effects on clinical outcomes according to how large is the therapeutic range for a given drug in a given disease setting. Ovarian cancer is a quite chemosensitive disease, hence the prognostic impact of mild underdosing may be lower or completely absent.

In conclusion, differently from what has been found in the cytotoxic treatment of other types of cancer, our analysis does not confirm that CIN is useful as a prognostic factor for patients receiving first-line carboplatin-based chemotherapy for ovarian cancer.

Conflicts of interest

Dr. De Placido reports personal fees from Roche, personal fees from Novartis, personal fees from Pfizer, personal fees from Celgene, personal fees from Astra-Zeneca, personal fees from Eisai, outside the submitted work.

Dr. Lorusso reports grants and personal fees from Tesaro, personal fees from Astra-Zeneca, grants and personal fees from Merck, grants and personal fees from Clovis, personal fees from Merrimack, outside the submitted work.

Dr. Piccirillo reports personal fees and travel support from Astra-Zeneca, personal fees from MSD, and travel support from Bayer.

Dr. Perrone reports personal fees and nonfinancial support from Bayer, personal fees from Ipsen, personal fees from Astra-Zeneca, personal fees from Bristol Myers Squibb, personal fees from Sandoz, personal fees from Incyte, personal fees from Celgene, personal fees from Pierre Fabre, personal fees from Janssen Cilag, outside the submitted work.

Dr. Pignata reports research grants and personal fees Roche, personal fees from Astra-Zeneca, personal fees from Clovis, personal fees from Tesaro, personal fees from MSD, personal fees from Merck, personal fees from Pharmamar, research grant from Shering Plough, outside the submitted work.

All the other authors have nothing to disclose.

Author contribution

Gennaro Daniele, Laura Arenare, Clorinda Schettino, Maria Carmela Piccirillo, Francesco Perrone, Ciro Gallo, and Sandro Pignata planned the study, pooled the data and produced initial draft.

Laura Arenare, Lorenzo Guizzaro, and Ciro Gallo performed statistical analysis.

Giovanni Scambia, Carmela Pisano, Roberto Sorio, Enrico Breda, Sabino De Placido, Antonella Savarese, Gabriella Ferrandina, Francesco Raspagliesi, Pierluigi Benedetti Panici, Antonella Ferro, Anita Rimanti, Gennaro Cormio, Domenica Lorusso, Sabrina Chiara Cecere, Simona Scalone, Valentina Angela Marsico, Cinzia Cardalesi, Francesco Cognetti, Vanda Salutari, Laura Attademo, and Sandro Pignata actively enrolled patients in the two pooled trials.

All the authors read and approved the final article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.04.012.

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