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Role of intraperitoneal chemotherapy in ovarian cancer in the platinum-taxane-based era: A meta-analysis

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ABSTRACT

Purpose: Intravenous (IV) chemotherapy has been compared with intraperitoneal (IP) chemotherapy in randomized clinical trials in advanced ovarian cancer (OC). The aim of this meta-analysis was to evaluate efficacy and toxicity of IV and IP and identify differences in outcomes.

Methods: The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was applied. Random-effects models were used. Primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS) and the proportion of patients with grade ≥2 acute toxicity.

Results: Four randomized clinical trials representing 2461 patients were identified. The hazard ratio (HR) of PFS was 0.88 (95% CI 0.80–0.98; $p = 0.01$, $I^2 = 24\%$) in favor of IP chemotherapy. IP chemotherapy was also associated with significant OS improvement compared with IV chemotherapy, with HR of 0.79 (95% CI 0.67–0.92; $p = 0.003$, $I^2 = 0\%$). Globally, grade ≥2 toxicities were reduced with IV chemotherapy.

Conclusion: This meta-analysis shows the superiority of IP chemotherapy over IV infusion in terms of clinical outcomes but toxicity rates. Its precise role in the management of advanced OC remains to be determined.

1. Introduction

At present, radical surgery, if possible, followed by platinum-taxane-based chemotherapy (CHT) is the standard of care in advanced ovarian cancer (OC) management (NCCN, 2018). Due to its specific natural history, OC is believed to be an ideal candidate for IP schemes and, therefore, CHT should be given as intraperitoneal (IP) or intravenous (IV) infusion. Over the years, several randomized clinical trials have assessed these infusion strategies and provided conflicting results regarding survival rates, mostly because of treatment heterogeneity (Alberts et al., 1996; Kirmani et al., 1994; Polyzos et al., 1999; Gadducci et al., 2000; Armstrong et al., 2006; Markman et al., 2001; Yen et al., 2001, 2009). However, these trials have confirmed that IP-CHT was usually associated with more frequent serious toxicity but similar or higher survival profile than IV-CHT (Jaaback et al., 2016).

Considering that several new trials have been published since the platinum-taxane-based CHT standardization, we provide an update, in order to provide a direct comparison of IP versus IV within the context of platinum-taxane-based trials and evaluate the superiority of one infusion regimen over the other.

2. Methods

2.1. Data extraction and trials selection

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was followed to perform search strategy and selection processes (Moher et al., 2009). The meta-analysis included trials without any restrictions on publication date. Systematic literature electronic search was conducted in Pubmed, Embase and Cochrane controlled trials meta-register and meeting proceedings for randomized clinical trials published or presented up to October 04, 2018. Literature search was performed using the following combinations of research criteria: "ovarian cancer", "intraperitoneal", "intravenous", "chemotherapy", "carboplatin", "cisplatin", "platinum", "taxane", "paclitaxel", "phase III", "randomized", "survival", "toxicity",

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Table 1
Details of the included trials.

Author	Year of publication	Study ID	Patients		Treatment		Median FU	Primary end point	Consideration
			IP	IV	IP	IV			
Markman et al. (2001)	2001	GOG 114	235	227	Carboplatin AUC 9 and paclitaxel 135 mg/m^2 (IV) + cisplatin 100 mg/m^2 (IP)	Cisplatin 75 mg/m^2 + paclitaxel 135 mg/m^2	N/A	PFS and OS	18.3% of IP patients received ≤ 2 cycles
Armstrong et al. (2006)	2006	GOG 172	205	210	Paclitaxel 135 mg/m^2 (IV) + cisplatin 100 mg/m^2 and paclitaxel 60 mg/m^2 (IP)	Cisplatin 75 mg/m^2 + paclitaxel 135 mg/m^2	50.4 months	PFS and OS	42% of IP patients completed 6 cycles
Provencher et al. (2018)	2018	OV21/ PETROC	102	101	Paclitaxel 135 mg/m^2 (IV) + carboplatin AUC 5/6 and paclitaxel 60 mg/m^2 (IP)	Carboplatin AUC 5/6 + paclitaxel 135 mg/ m^2	33 months	PD9	7.6% of IP patients discontinued treatment
Walker et al. (2016)	2016	GOG 252	464[a]	461	Carboplatin AUC 6 (IP) + paclitaxel 80 mg/m^2 and bevacizumab 15 mg/kg (IV)	Carboplatin AUC 6 + paclitaxel 80 mg/m^2 + bevacizumab 15 mg/kg	N/A	PFS	90% of IP patients completed 6 cycles of platinum
			456[a]	461	Paclitaxel 135 mg/m^2 (IV) + cisplatin 75 mg/m^2 and paclitaxel 60 mg/m^2 (IP) + bevacizumab 15 mg/kg (IV)	Carboplatin AUC 6 + paclitaxel 80 mg/m^2 + bevacizumab 15 mg/kg	N/A	PFS	84% and 87% of IP patients completed 6 cycles of platinum and taxane, respectively

ID: identifier; IP: intraperitoneal; IV: intravenous; FU: follow-up; GOG: Gynecologic Oncology Group; AUC: area under the curve; mg: milligrams; m^2: square meter; N/A: not available; PFS: progression-free survival; OS: overall survival; PD9: 9-month progressive disease rate; kg: kilograms.

[a] Included "exploratory" cases: suboptimal (7%) and stage IV (5%).

"quality of life". Search strategy was devised based on the Cochrane highly sensitive search strategy (Lefebvre et al., 2011).

To be eligible, published and unpublished trials had to compare IP-CHT and IV-CHT in OC treatment. Randomized clinical trials including a standard CHT regimen, defined as platinum-taxane-based, written in English, were included. Reference lists of previously published narrative or systematic reviews and meta-analysis were explored. Retrospective studies, case series, case reports, commentaries and letters to editors were excluded.

Two independent reviewers (CM and FDF) selected the identified studies based on the title and abstract. If the topic of the study could not be ascertained from its title or abstract, the full-text version was retrieved for evaluation. Disagreement was resolved with a third party (LM).

Trials were eligible if participants were newly diagnosed, with histologically proven epithelial OC, primary peritoneal or fallopian tube carcinoma at study entry. In closer evaluation of potentially eligible articles, when two articles appeared to report results with overlapping data, only the data representing the most recent publication were included in the meta-analysis. Extracted data were recorded into standardized database according to the following parameters: first author's surname, year of publication, study identifier, sample size of IP group and IV group, treatment, duration of follow-up, clinical outcomes.

2.2. PICO question

In patients with epithelial OC, primary peritoneal or fallopian tube carcinoma suitable for standard CHT followed by surgery, does the use of IP-CHT compared to IV-CHT improve progression-free survival, overall survival and reduce toxicity?

2.3. Primary and secondary outcomes

The intent of the analysis was to evaluate progression-free survival (PFS). We also planned to analyze overall survival (OS) and the proportion of patients with grade ≥2 acute toxicity. Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) (CTEP, 2018). The definition of both PFS and OS was similar across trials. PFS and OS were defined as time from the date of randomization to the defined event using Kaplan–Meier method. The hazard ratio (HR) and the number of events (death and progression), when available, were derived from each study. At least one of these three outcomes should have been assessed and reported in the trial to be included in the present analysis.

2.4. Statistical analysis

The grading of recommendations assessment, development and evaluation (GRADE) system was used to rate quality of evidence and grade strength of recommendations for all included studies (Guyatt et al., 2011). Statistical analysis was performed using Review Manager 5.0 (http://www.cochrane.org). The pooled HR and risk ratio (RR) were calculated using a fixed- or random-effects model. Forest plots were used for graphical representation of each study and pooled analysis. The size of each box represents the weight that the corresponding study exerts in the meta-analysis; confidence intervals (CI) for each study are displayed as a horizontal line through the box. The pooled HR and RR are symbolized by a solid diamond at the bottom of the forest plot, and the width of the square represents the 95% CI of the HR and RR. HR, RR and 95% CI, for each study were extracted or calculated, based on the published studies, according to the methods described by Tierney et al. (2007). A significant two-way p value for comparison was defined as $p < 0.05$. Statistical heterogeneity among studies was examined using both the Cochrane Q statistic (significant at $p < 0.1$) and the I^2 value (significant heterogeneity if > 50%) (Higgins et al., 2003).

3. Results

3.1. Studies selection and characteristics

We identified 9 randomized clinical trials that were potentially eligible (Alberts et al., 1996; Kirmani et al., 1994; Gadducci et al., 2000; Armstrong et al., 2006; Markman et al., 2001; Yen et al., 2001, 2009; Provencher et al., 2018; Walker et al., 2016). We did not collect data from 5 trials because the studies used non-standard CHT regimen (Alberts et al., 1996; Kirmani et al., 1994; Gadducci et al., 2000; Yen et al., 2001, 2009). Update data could be obtained for two trials, but it was a post hoc analysis using pooled data from all patients enrolled into GOG 114 and GOG 172 protocols and patients were submitted to different drug schedule. Therefore this study was excluded after independent review (Tewari et al., 2015a). Overall, 4 randomized clinical trials (3 published and 1 unpublished) representing 2461 patients were included in the meta-analysis (Armstrong et al., 2006; Markman et al., 2001; Provencher et al., 2018; Walker et al., 2016). Details are listed in Table 1. PFS was the primary end point for all studies but one, which evaluated 9-month progressive disease (PD9) rate as primary outcome of interest. Results of the quality of each included stud is classified as having a low to unclear risk of bias (Supplement Figure 1).

3.2. Primary outcome

Overall, 1551 of 2461 patients had a disease progression or died. Compared to IV-CHT, IP-CHT had a significant effect on PFS (HR 0.88, 95% CI 0.80–0.98; $p = 0.01$) (Fig. 1). Heterogeneity between trials was not significant ($I^2 = 24\%$). The effect on PSF of two IP drugs – platinum and taxane – with or without bevacizumab was not significant (HR 0.90, 95% CI 0.78–1.03) (Supplement Figure 2). The PFS benefit was restricted to the IP-CHT regimens without bevacizumab (Figs. 2 and 3). The use of single – platinum – and/or double – platinum-taxane – agents did not change the significance of the PFS effect of the IP-CHT treatment (HR 0.79, 95% CI 0.69–0.90 and HR 0.81, 95% CI 0.67–0.97, respectively). There was no substantial heterogeneity ($I^2 = 0\%$) for both subgroup analysis.

The quality of evidence and strength of recommendation for the primary outcome is summarized in Table 2.

3.3. Secondary outcomes

Data regarding OS were available in three studies (Armstrong et al., 2006; Markman et al., 2001; Provencher et al., 2018). A significant OS increase favoring IP-CHT was observed: HR 0.79, 95% CI 0.67–0.92 ($p = 0.003$; $I^2 = 0\%$).

Grade ≥2 toxicity analysis mainly demonstrated a benefit in favor of the IV-CHT. Interestingly, the risk of neuropathy (HR 1.26, 95% CI 0.80–1.96), fatigue (HR 1.75, 95% CI 0.41–7.42), febrile neutropenia (HR 1.03, 95% CI 0.51–2.06) and thrombocytopenia (HR 1.90, 95% CI 0.48–7.57) were not consistently and significantly reduced with IV-CHT infusion. Details are presented in Fig. 4.

4. Discussion

In our meta-analysis we have demonstrated that IP-CHT based on the association of taxane with a platinum compound is an effective and reasonably safe approach in the treatment of advanced OC.

The role of IP-CHT in advanced OC treatment is still controversial. Although its benefit has been described in different trials (Alberts et al., 1996; Kirmani et al., 1994; Polyzos et al., 1999; Gadducci et al., 2000; Armstrong et al., 2006; Markman et al., 2001; Yen et al., 2001, 2009; Provencher et al., 2018; Walker et al., 2016), the use of IP-CHT has not been fully accepted or incorporated into current care, despite a statement of the National Cancer Institute promoting its use in women with advanced OC (NCI, 2018). Here, we analyzed data of the more recent trials on this topic, including only those studies in which the IV-CHT arm was based on paclitaxel plus a platinum compound, resembling our current standard treatment. Looking at their data and study design, some pitfalls have emerged (Table 1). First of all, in 3 out of 4 trials, the IV-CHT arm was not the standard treatment, defined as IV paclitaxel 175 mg/m^2 and carboplatin AUC 5–6 administered every 3 weeks, as recommended by the 5th Ovarian Cancer Consensus Conference (OCCC) (Karam et al., 2017). Secondly, in all trials but one the IP-CHT schedules included both taxane (paclitaxel) and platinum (carboplatin or cisplatin) by IP infusion (Armstrong et al., 2006; Provencher et al., 2018; Walker et al., 2016), whereas in the GOG 114 study (Markman et al., 2001) patients received only cisplatin 100 mg/m^2 IP. Lastly, drugs doses and timing of administration were different across all trials analyzed, especially with regard to cisplatin dosage (Armstrong et al., 2006; Markman et al., 2001; Provencher et al., 2018; Walker et al., 2016).

In our analysis we found that IP-CHT allowed an improvement of both OS (HR 0.79, 95% CI 0.67–0.92) and PFS (HR 0.88, 95% CI 0.80–0.98) over IV-CHT in advanced OC management. Nevertheless, survival data from OV21/PETROC and GOG 252 studies are still immature and therefore results should be considered with caution (Provencher et al., 2018; Walker et al., 2016). Besides, we tried to define whether the addition of a taxane – paclitaxel – is recommendable, as suggested by the 5th OCCC (Karam et al., 2017). Interestingly, when considering all together those trials which used the doublet of paclitaxel with a platinum compound, we only found a slight trend toward IP administration (HR 0.90, 95% CI 0.78–1.03) but when we limited our analysis to those studies who received both drugs by the IP route without IV bevacizumab, the PFS was significantly increased (HR 0.81, 95% CI 0.67–0.97). Up to now, only the GOG 252 study proposed the association of bevacizumab to standard CHT in both IP and IV arms (Walker et al., 2016). Interestingly, it was the only negative study. However, the addition of bevacizumab to weekly paclitaxel in the IV-CHT arm is quite debatable, due to its proven increased toxicity rate without any survival benefit (Chan et al., 2016). Moreover, as suggested in the GOG 262 trial, the addition of bevacizumab to both IP-CHT and IV-CHT schemes may have equalized the dose-dense paclitaxel effect over the every 3 week paclitaxel (Chan et al., 2016). In addition, dose reduction of cisplatin and paclitaxel may have diminished the superiority of IP therapy and the inclusion of suboptimal and stage IV disease patients may have attenuated IP therapy which has been proven to be most effective in those with minimal residual disease (Monk and Chan, 2017).

With regard to toxicities, our results are in agreement with the general reasonable assumption that IV plus IP chemotherapy is more toxic then IV alone and that is quite unusual for patients receiving both

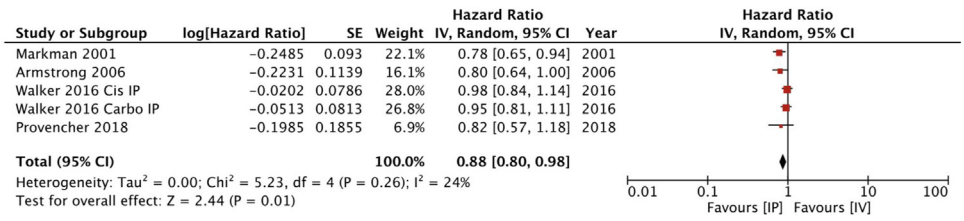

Fig. 1. Forest plot of progression-free survival of all included studies.

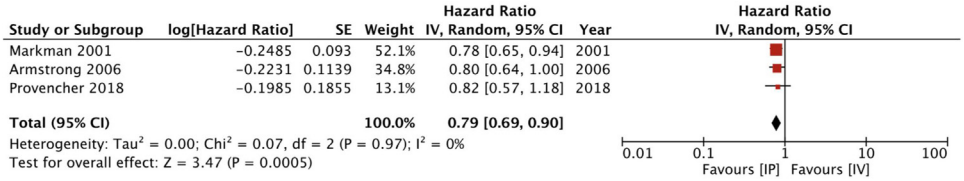

Fig. 2. Forest plot of progression-free survival of studies using platinum-based or taxane-platinum-based intraperitoneal chemotherapy.

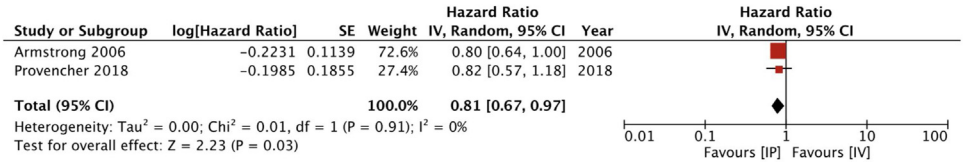

Fig. 3. Forest plot of progression-free survival of studies using taxane-platinum-based intraperitoneal chemotherapy.

Table 2
Quality of evidence and strength of recommendation: summary of findings.

IP-CHT compared to IV-CHT in advanced ovarian cancer

Patient or population: advanced ovarian cancer
Setting:
Intervention: IP-CHT
Comparison: IV-CHT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with IV-CHT	Risk with IP-CHT				
Progression-free survival (PFS) assessed with: Kaplan–Meier Product Limit	65 per 100	**60 per 100** (57 to 64)	**HR 0.88** (0.80 to 0.98)	2461 (4 RCTs)	⊕⊕⊕⊕ High[a]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Unclear risk of detection bias in several studies may not be downgraded.

IP and IV to complete all the pre-determined cycles of chemotherapy. Several clinical factors, both treatment-related (surgical approach, CHT access) and patient-related (age, mutational status), should be considered to better select cases who could well-tolerate IP-CHT infusion. For instance, colonic resection is associated with high rate of treatment suspension, mainly due to local complications or upper abdominal tumor metastasis (Armstrong et al., 2006; Jaaback et al., 2011; Yen et al., 2009). In order to reduce the risk of catheter-related complications and decrease IP-CHT discontinuation different way of IP-CHT infusion, such as ultrasound-guided direct puncture, should be proposed (Benedetti-Panici et al., 2012). Also patient age should represent a decisional factor. Prognosis in elderly patients with clear cell tumors is poor and IP-related toxicities would be probably exceed its potential benefit (Jaaback et al., 2011; Yen et al., 2009). Differently, younger patients seem to be more likely to complete the six cycles of IP regimen, and the risk of death is decreased by 12% for each additional IP cycle (Tewari et al., 2015b).

Another consideration should be about BRCA status. In fact, BRCA1 mutations carriers seem to be particularly sensitive to IP-CHT (Konstantinopoulos et al., 2010). In GOG 172 study, patients BRCA1 status was examined (Lesnock et al., 2013). Abnormal BRCA1 expression in IP-CHT was associated with significantly higher OS versus BRCA mutations carriers in IV-CHT group. Whereas, in those patients with normal BRCA1 expression, OS was similar when comparing IP-CHT versus IV therapy. Therefore, it is reasonable that BRCA mutation carriers, who are known to have an increased platinum sensitivity, should particularly benefit to the highest platinum dose intensity resulting from IP infusion.

Globally, drugs and schedules of administration were uneven precluding a rigorous comparison between studies. It has been hypothesized that treatment efficacy in GOG 252 trial has been impaired by cisplatin dose-reduction, that was planned to reduce toxicity (Monk and Chan, 2017). Final results of GOTIC-001/JGOG-3019 study would probably resolve several of these issues, albeit IP arm will receive only carboplatin IP infusion, without IP paclitaxel (http, 0000).

Based on positive results of this meta-analysis, we believe that toxicity is not enough to abandon IP route of administration. Would we spared surgical radical cytoreduction to OC patients because it is more complicated? Even after the publication of the “neoadjuvant” trials (Vergote et al., 2010; Kehoe et al., 2015) we are still facing with the opportunity to perform primary debulking surgery instead of interval debulking, and we have tried to improve our surgical skills, more than lessening our radicality in cytoreduction. Probably we should aim to the same challenges even with the IP infusion, in order to find a balance between right effective doses and tolerable toxicity. Probably, effective and safe delivery of intraperitoneal chemotherapy requires the multidisciplinary expertise of a skilled team, more easily available in high-volume centers.

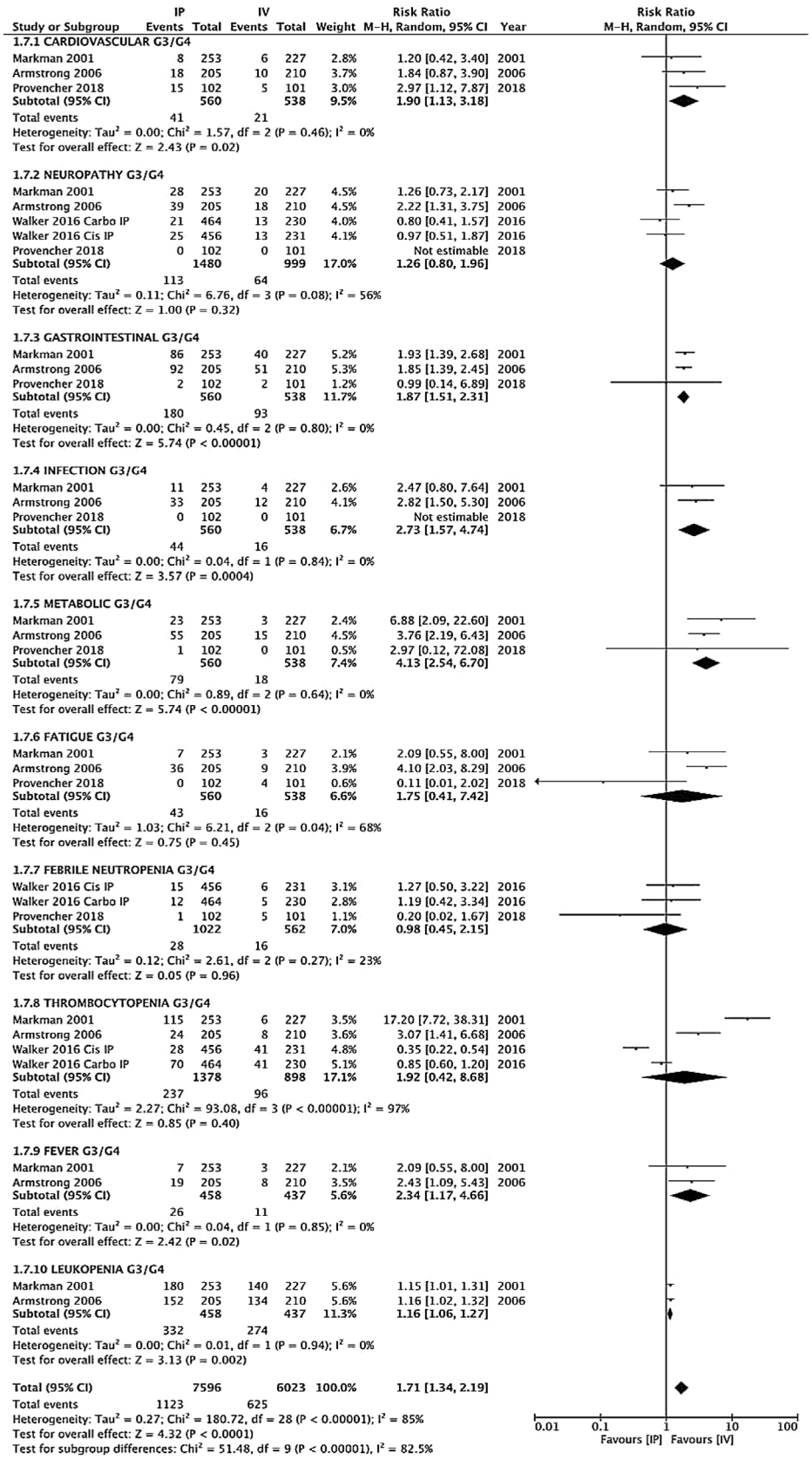

Fig. 4. Forest plot of toxicity profile.

Our meta-analysis is based only on randomized clinical trials included platinum-taxane-based CHT strategy. But there was some heterogeneity among drug doses and schedule used in trials. This meta-analysis could not assess the real impact of IP-CHT on toxicity because it wasn't a primary endpoint in any of the included trials, preventing any possible definitive conclusions. Another limitation of this meta-analysis is that both timing and surgical characteristics were not considered. Data were not enough to define the influence of these surgical debulking factors. However the quality of studies for clinical outcomes were not downgraded due to high-risk of bias. Globally there is consistent moderate-quality evidence that IP-CHT significantly improve PFS in advanced OC patients over IV-CHT. The potential addition of GOTIC-001/JGOG-3019 study, as well as improved data of long-term outcomes of these included trials should be necessary to validate our results and confirm the power of this meta-analysis. Also a cost-effectiveness analysis should be useful.

5. Conclusion

This meta-analysis demonstrated that IP-CHT in advanced OC management increased survival outcomes, especially PFS. The association of IP paclitaxel with an IP platinum compound might represent the right choice and should be offered as a treatment option in some well defined patients, such as young BRCA1 mutations carries. Further researches should be based on trials design aimed to identify the best IP schedule and the less toxic IP access way of administration to personalize treatment.

Conflicts of interest

None.

Acknowledgment

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.critrevonc.2019.01.002.

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