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IMPACT OF COMBINATION CHEMOTHERAPY ON TOXICITY IN OVARIAN CANCER: SYSTEMATIC REVISION OF LITERATURE AND META-ANALYSIS

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ABSTRACT

The purpose of this statistical analysis is to demonstrate the real advantages in terms of cost-benefit of combination chemotherapy compared with single-agent chemotherapy. The trials, which are used in this meta-analysis, have been searched on PubMed database and they are phase II or randomized phase III studies with only chemotherapy regimens. In this meta-analysis were evaluated adverse effects with odds ratio (OR), which is expressed in 95% confidence intervals (95% CI). Only 4 studies contained all the set selection criteria and they were selected. The data, which were obtained, were analyzed using MedCalc Application. The combination therapy was more strongly linked to certain adverse events than to chemotherapy with a single agent: thrombocytopenia, anemia, neutropenia and nausea. The data obtained for leukopenia, for vomiting and for stomatitis are not statistically significant, as well as those of antitumor activity. Obtained data allow us to state that the overall combination therapy is more closely related to adverse effects such as thrombocytopenia, anemia, neutropenia and nausea compared tosingle-agent chemotherapy.

Keywords*: ovarian cancer, toxicity, single-agent chemotherapy, combination chemotherapy, meta-analysis.*

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Introduction

Ovarian cancer is the second among gynecologic malignancies in order of frequency and in Italy it is estimated about 5,000 new cases a year.

Ovarian cancer is the leading cause of death among gynecologic cancer (3000 patients each year die from the disease) and represents 5% of all cancers[(1)].

The occurrence of cancer is related to exposure to risks of various kinds, among whom there are prolonged hormonal action (Fathalla theory), use of drugs that stimulate ovulation, obesity and, especially, advanced age[(2)]. In fact, ovarian cancer is defined as a cancer whose incidence rises with increasing age: the peak was found at 63 years, but cases of ovarian cancer increased from 40 years onwards[(2)]. fig

However, there are cases in which the tumor is diagnosed in young women and this is due to a genetic predisposition with alterations of certain genes, such as the BRCA 1 and 2. Currently the standard treatment approach involves surgical excision of the tumor (when feasible) possibly associated with therapy with Carboplatin as a single agent or in combination with Paclitaxel.

Other drugs have been tested and are currently administered in case of resistance or contraindications (such as adverse reactions) to therapy with carboplatin and paclitaxel, such as Docetaxel, Doxorubicin Liposomal Pegylated, Gemcitabine, Epirubicin and Trabectedin[(3-4-5-6-7-8)].

In recent years have been also introduced targeted agents (Bevacizumab, Olaparib, Pazopanib, Cediranib) in the treatment of ovarian cancer with promising results[(9)].

The stage classification more frequently used is International Federation of Gynecology and Obstetrics (FIGO) staging, based on clinical criteria and especially on surgical staging.

Material and methods

In this meta-analysis, we wanted to analized the impact of toxicity of combination therapy towards the monotherapy in ovarian cancer.

Search strategy

The search for the selection of trials and studies related to the meta-analysis we consulted PubMed database with the last updated on April 2015.

The research contained the terms "ovarian cancer" AND "chemotherapy" and the results were individually scanned against the selection criteria set after the search, which allowed to exclude or select various studies according to their characteristics and their inherence the selection criteria.

Selection criteria

• Randomized trials (Phase IIR studies and phase III);

• Trials that included only chemotherapy regimens;

• Trials comparing monotherapy and combination chemotherapy;

• Trials that included toxicity data in various systems and devices.

From the initial search of PubMed database emerged 13854 results that by applying gradually the various selection criteria, have been reduced first to 195 and then eventually only four have met all the criteria (Fig 1).

The selected studies included a total of 1553 patients, of course all female, who had attained the age of eighteen.

The items individually showed a variable number of patients: the study with fewer patients had 165, the most numerous 672 patients.

The selected trials are three phase III studies and one phase II randomized study; in addition, among the four trials selected, two studies are at two-arm trials and the other two are three-arm trials, ie, the first compare two populations of patients and seconds three populations of patients.

The obtained results from the selection of the studied articles were carefully analyzed and extracted data were compared in the trials selected.

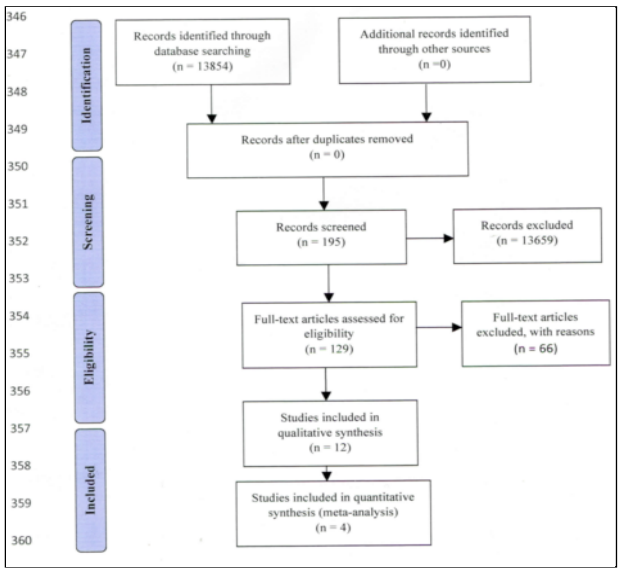

Figure 1: Studies selection.

TROMBOCITOPENIA	Mono N	Mono X	Combo N	Combo X
PLD vs PLD+trabectedina (OVA-301)	330	4	333	23
Topotecano vs Topotecano+Etoposide	178	24	177	38
Topotecano vs Topotecano+Gemcitabina	178	24	147	46
PLD vs PLD+trabectedina (Barkley Monk J et al.)	330	8	333	61
Paclitaxel vs Paclitaxel+Carboplatino	56	1	51	2
Paclitaxel vs Paclitaxel+Topotecano	56	1	57	4

Table 1: Thrombocytopenia. N: total number of patients; X: the number of patients who experienced the side effect; Mono: single-agent therapy; Combo: combination therapy.

By comparing the various studies were considered particular adverse events, such as thrombocytopenia, anemia, leukopenia, neutropenia, nausea, vomiting and stomatitis, while data on the adverse event diarrhea were not sufficient to carry out the analytical comparison between studies.

In all studies, the data concerning the side effects considered the toxicity of grade 3 and grade 4; only data on vomiting in one of four studies also include patients with the side effect of grade 2 (Tab 1-2-3-4-5-6-7).

Moreover, in some of the selected studies, was evaluated and analyzed the antitumor activity in patients examined, in terms of "partial response" (PR) and "complete response" (CR) (Tab 8).fig

The data extrapolated for adverse events and antitumor activity were included in the Excel tables, where they were confronted the effects of

combination therapy and those of monotherapy for every single side effect. The tables are listed in the Appendix (Tab 1-8).

ANEMIA	Mono N	Mono X	Combo N	Combo X
PLD vs PLD+trabectedina (OVA-301)				
Topotecano vs Topotecano+Etoposide	178	33	177	53
Topotecano vs Topotecano+Gemcitabina	178	33	147	26
PLD vs PLD+trabectedina	330	16	333	41
Paclitaxel vs Paclitaxel+Carboplatino	56	3	51	10
Paclitaxel vs Paclitaxel+Topotecano	56	3	57	17

Table 2: Anemia. N: total number of patients; X: the number of patients who experienced the side effect; Mono: single-agent therapy; Combo: combination therapy.

NEUTROPENIA	Mono N	Mono X	Combo N	Combo X
PLD vs PLD+trabectedina (OVA-301)	330	30	333	72
Topotecano vs Topotecano+Etoposide				
Topotecano vs Topotecano+Gemcitabina				
PLD vs PLD+trabectedina (Barkley Monk J et al.)	330	74	333	209
Paclitaxel vs Paclitaxel+Carboplatino	56	7	51	28
Paclitaxel vs Paclitaxel+Topotecano	56	7	57	24

Table 3: Neutropenia. N: total number of patients; X: the number of patients who experienced the side effect; Mono: single-agent therapy; Combo: combination therapy.

LEUCOPENIA	Mono N	Mono X	Combo N	Combo X
PLD vs PLD+trabectedina (OVA-301)				
Topotecano vs Topotecano+Etoposide	178	92	177	108
Topotecano vs Topotecano+Gemcitabina	178	92	147	47
PLD vs PLD+trabectedina(Barkley Monk J et al.)	330	32	333	110
Paclitaxel vs Paclitaxel+Carboplatino	56	4	51	16
Paclitaxel vs Paclitaxel+Topotecano	56	4	57	15

Table 4: Leukopenia. N: total number of patients; X: the number of patients who experienced the side effect; Mono: single-agent therapy; Combo: combination therapy.

NAUSEA	Mono N	Mono X	Combo N	Combo X
PLD vs PLD+trabectedina (OVA-301)	330	2	333	9
Topotecano vs Topotecano+Etoposide	178	5	177	12
Topotecano vs Topotecano+Gemcitabina	178	5	147	8
PLD vs PLD+trabectedina(Barkley Monk J et al.)	330	8	333	29
Paclitaxel vs Paclitaxel+Carboplatino				
Paclitaxel vs Paclitaxel+Topotecano				

Table 5: Nausea. N: total number of patients; X: the number of patients who experienced the side effect; Mono: single-agent therapy; Combo: combination therapy.

VOMITING	Mono N	Mono X	Combo N	Combo X
PLD vs PLD+trabectedina (OVA-301)	330	2	333	111
Topotecano vs Topotecano+Etoposide	178	7	177	11
Topotecano vs Topotecano+Gemcitabina	178	7	147	4
PLD vs PLD+trabectedina(Barkley Monk J et al.)	330	7	333	34
Paclitaxel vs Paclitaxel+Carboplatino	56	10	51	13
Paclitaxel vs Paclitaxel+Topotecano	56	10	57	14

Table 6: Vomiting. N: total number of patients; X: the number of patients who experienced the side effect; Mono: single-agent therapy; Combo: combination therapy.

STOMATITI	Mono N	Mono X	Combo N	Combo X
PLD vs PLD+trabectedina (OVA-301)	330	6	333	1
Topotecano vs Topotecano+Etoposide	178	0	177	2
Topotecano vs Topotecano+Gemcitabina	178	0	147	0
PLD vs PLD+trabectedina(Barkley Monk J et al.)	330	17	333	3
Paclitaxel vs Paclitaxel+Carboplatino				
Paclitaxel vs Paclitaxel+Topotecano				

Table 7: Stomatitis. N: total number of patients; X: the number of patients who experienced the side effect; Mono: single-agent therapy; Combo: combination therapy.

Statistical analysis

The data included in the tables for each side effect and for the antitumor activity were included in the free trial version of the program "MedCalc application", Copyright © 1999-2016 MedCalc.com

ANTITUMOR ACTIVITY	Mono N	Mono PR+CR	Combo N	Combo PR+CR
Paclitaxel vs Paclitaxel+Carboplatino	57	20	51	19
Paclitaxel vs Paclitaxel+Topotecano	57	20	57	22
Topotecano vs Topotecano+Etoposide	133	37	122	44
Topotecano vs Topotecano+Gemcitabina	133	37	95	30

Table 8: Antitumor activity. N: total number of patients; X: the number of patients who experienced the side effect; Mono: single-agent therapy; Combo: combination therapy.

The parameters of the tables have been included in the application, in such a way to be considered as a "control group" patients who had carried out as monotherapy and "intervention group" patients who were subjected to combination therapy.

After entering the data, for each side effect and for the antitumor activity, the meta-analysis was performed, with the calculation of odds ratios (OR) and the automatic construction of graphics. In this meta-analysis, the OR is used to evaluate the actual link between the combination of drugs used and the occurrence of the side effect and the answer to given by the values of OR obtained.

The values of OR <1 indicates that the factor under consideration, namely the combination therapy, appears to be protective against the side effect and that monotherapy exposed to a higher risk of onset of the side effect.

The values of OR> 1, by contrast, demonstrate that the combination therapy is closely related to the pathogenesis and the onset of the side effect, while for values of OR=1 the adverse effect appears independently from exposure to chemotherapy single- agent or combination[9-10-11].

The confidence interval (CI) provides a range of possible values within which it is estimated to fall, with a probability level chosen at will, the true value of the parameter considered in the population.

Actually we are not sure that the sample is included in this range, but there is a 95% probability that it is (95% CI)[13-14].

The heterogeneity of the included studies was tested using the Cochran Q test, with a significance level set to 0.1. The meta-analysis of OR was performed to calculate the pooled OR, using the random effect or the fixed effect, depending on the statistical significance of the Q-test, according to the method of Mantel-Haenszel test.

Results

Studies selected

Selected studies show the comparison between the chemotherapy with a single agent and that of combination, and in particular:

• The study of Monk B.J. et al.[15] compared therapy with pegylated liposomal doxorubicin as a single agent and its combination with trabectedin in patients with recurrent ovarian cancer, after failure of first-line therapy with platinum-based chemotherapy regimens;

• The study CARTHAXY carried out by the GINECO group[16] compares treatment with paclitaxel as a single agent and its combination with topotecan and with carboplatin in patients with relapsed ovarian cancer, after the first or second line chemotherapy with platinum and taxane-based, with disease progression within 6 months after the last treatment cycle;

• The study OVA-301[17] compares the therapy with pegylated liposomal doxorubicin as a single agent and its combination with trabectedin in patients with recurrent cancer after treatment with platinum-based regimens, in the presence of platinum-sensitive or partially platinum-sensitive cancer;

• The study of German society NOGGO[18] compares the single-agent therapy with topotecan and its combination with etoposide and with gemcitabine in patients with recurrent cancer after being treated with primary surgical approach and chemotherapy (platinum-based regimens).

The data on toxicity and on antitumor activity were analyzed using MedCalc application, that has allowed us to study all the individual aspects examined.

They were considered total values random-effects, for the results that showed a p-value <0.1, as with significant heterogeneity in terms of statistics; they were considered instead the total values fixed-effects for those who had a p-value> 0.1, because not significant from the point of view of heterogeneity[14].

Thrombocytopenia

The analysis found a statistically significant (OR: 3.722; 95% CI: 1.987 to 6.974) regarding the parameter thrombocytopenia compared in the two patient populations analyzed. It is shown that, overall, thrombocytopenia occurs more frequently in patients undergoing combination therapy compared

to patients which is administered therapy with a single agent. The pooled OR for thrombocytopenia was calculated using the random effect, because of significant heterogeneity between studies (P <0.001) (Fig 2).

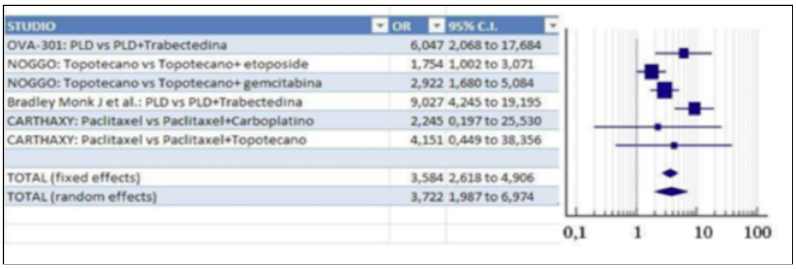

Fig 2: Thrombocytopenia: meta-analysis results.

Anemia

Statistical analysis showed a significant result (OR: 2.298; 95% CI: 1.259 to 4.193) of the parameter anemia in comparing the combination regimens and those monotherapy. The pooled OR for anemia was calculated using the random effect, due to the significant heterogeneity among the studies (P = 0.007) (Fig 3).

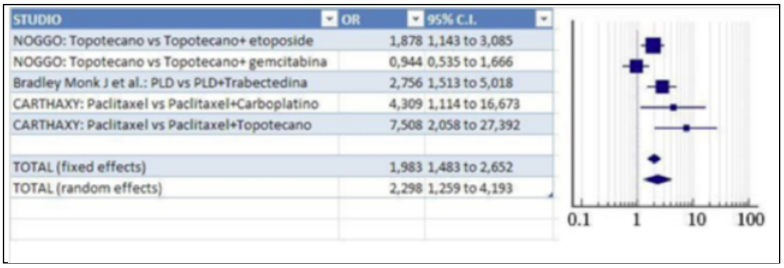

Fig 3: Anemia: meta-analysis results.

Neutropenia

Results show statistical significance (OR: 4.794; 95% CI: 2.922 to 7.864) of the variable neutropenia in comparison between the combination and the monotherapy regimens.

All graphs for individual comparisons revealed greater frequency of neutropenia in the combination therapy compared to monotherapy.

The pooled OR for neutropenia was calculated using the random effect, because of significant heterogeneity between studies (P <0.001) (Fig 4).

Fig 4: Neutropenia: meta-analysis results.

Leukopenia

The results of the meta-analyzes highlight how the leukopenia data are not statistically significant, since the results are very heterogeneous.

The pooled OR for leukopenia was calculated using the fixed effect (OR: 1.719; 95% CI: 1.375 to 2.150), due to no significant heterogeneity between studies (P = 0.121). (Fig 5)

Nausea

The interpretation of the results (OR: 3.77; 95% CI: 1.822 to 5.197) shows that nausea is a side effect that increases in combination with chemotherapy regimens of two drugs. The pooled OR for nausea was calculated using the random effect, due to the significant heterogeneity among the studies (P <0.001) (Fig 6).

Vomiting

The data obtained from the meta-analysis showed a lack of statistical significance: OR: 3.093; 95% CI: 0.910 to 10.513. The pooled OR for vomiting was calculated using the random effect, because of significant heterogeneity between studies (P = 0.070) (Fig 7).

Stomatitis

The pooled OR for the stomatitis was calculated using the fixed effect, due to non-significant heterogeneity among the studies (P = 0.224).

Looking at the graph you can see that the overall results are not statistically significant (OR: 0.269; 95% CI: 0.113 to 0.644) (Fig 8).

Antitumor activity

The pooled OR for the antitumor activity was calculated using the fixed effect, due to non-significant heterogeneity among the studies (P = 0.150).

From data analysis findings are uncertain and not statistically significant (OR: 1.262; 95% CI: 0.920 to 1.734) (Fig 9).

Discussion

The standard treatment for ovarian cancer is carboplatin AUC 6 single-agent or carboplatin AUC 5 associated with paclitaxel 175 mg / m2.

Recurrence of ovarian cancer are also treated with platinum-based regimens (especially in platinum-sensitive cancers), but not platinum-based monotherapy is the preferred treatment in the platinum-resistant patients.

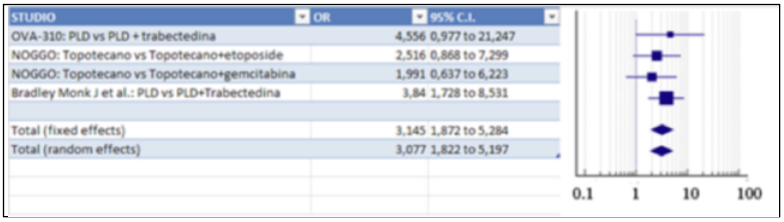

Fig 5: Leukopenia: meta-analysis results.

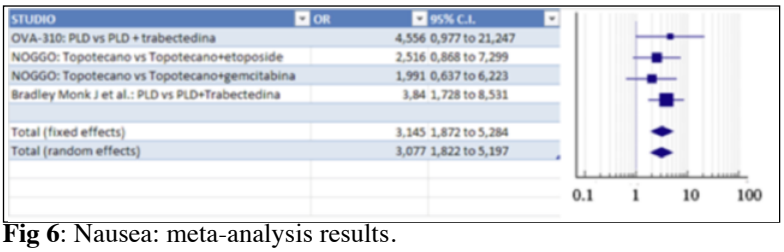

Fig 6: Nausea: meta-analysis results.

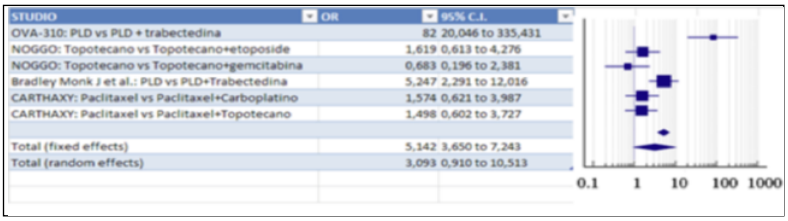

Fig 7: Vomiting: meta-analysis results.

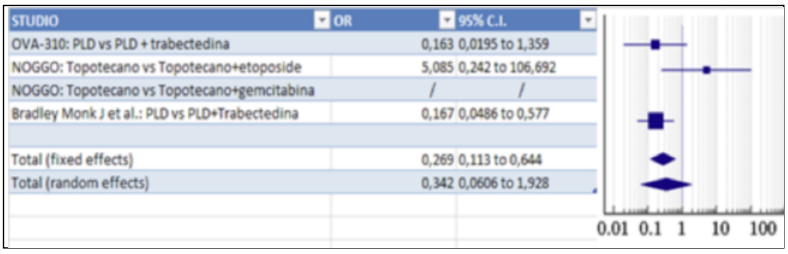

Fig 8: Stomatitis: meta-analysis results.

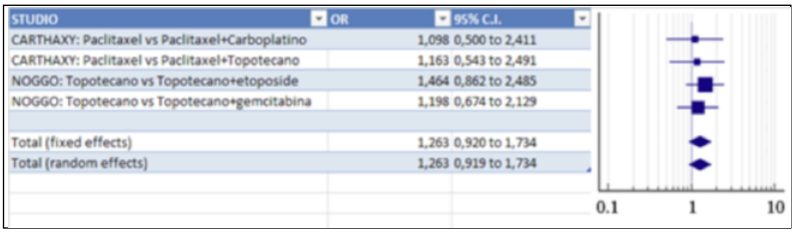

Fig 9: Antitumor activity: meta-analysis results.

Many physicians consider even a not platinum-based single-agent therapy in patients with platinum-sensitive cancer, since it has been demonstrated a greater benefit of further platinum-based treatment.

Studies of Huinink and Gordon assess the activity of paclitaxel, Liposomal Doxorubicin and Topotecan as single agents and the association of paclitaxel to carboplatin in platinum-sensitive and platinum-resistant patients, after a first treatment approach based on platinum. The results obtained show that the combination therapy is more strongly associated with improvements in terms of efficacy as measured both PFS (Progression Free Survival) and OS (Overall Survival)[15].

Carthaxy study compares three groups of patients treated respectively with weekly paclitaxel, with Topotecan and paclitaxel and with carboplatin and Paclitaxel. The data extrapolated from the study highlight that there are no significant differences between the three patient populations in terms of PFS and Response Rate. Therefore, schemes with weekly paclitaxel are preferred since at equal PFS and RR (Response Rate), are associated with less toxicity[16].

The study OVA-301 demonstrated greater efficacy of the combination of Doxorubicin Liposomal Pegylated with Trabectedin compared to only Doxorubicin Liposomal Pegylated. The increased effectiveness is evaluated in terms of OS, where there is a survival that increases of 3 months (19 VS 22 months): these data are more evident in platinum sensitive patients, where it is also noted a reduction in the risk of progression disease and death[17].

The study of the company NOGGO compares Topotecan as a single agent and its association with etoposide and with gemcitabine: single-agent regimens are considered standard treatment in second-line therapy in platinum-sensitive and platinum-refractory patients[18].

The studies do not give unanimous indication, both in terms of effectiveness, that of greater or less toxicity associated.

The latest evidence shows how in fact are encouraging data on regimens targeted agents, such as anti-VEGF Avastin, which results in improved survival of four months (12.4 VS 8.4) associated with the carboplatin or with other regimes of combination chemotherapy.

Results even more favorable has encountered Olaparib, a monoclonal antibody that inhibits PARP and DNA repair errors, in patients with mutations in the BRCA 1 and 2.

Olaparib reduces the risk of disease progression by 82% and determines an increase of PFS from 4.3 months to 11.2 months. The most significant findings were observed in patients treated with platinum-based regimens, which later have to answer they are exposed to Olaparib as maintenance therapy[19].

Conclusions

The systematic review of the literature and the subsequent meta-analysis performed by virtue of the data extrapolated from the four selected articles, gave very different results for the various parameters examined.

The results emerging from the analytical evaluation of the data associated with variables vomiting, leukopenia and stomatitis demonstrate how the features and values of the trails are not considered fit for the comparison.

The two three-arm studies also reported data inherent the anti-tumoral activity: analysis of this data does not allow assessing a better anti-tumoral activity of the combination therapy, compared to treatment with a single chemotherapeutic agent.

In the assessment of thrombocytopenia, neutropenia, anemia and nausea related data in combination therapy and in treatment to single pharmacological agent, the meta-analysis showed that globally these side effects are associated mainly to the combination of two drugs.

In conclusion, the analyzed data were extrapolated, however, regardless of the values of the response to therapy in terms of PFS and OS, so this goes in part to limit the decision on the most effective treatment regimen in patients with ovarian cancer. This meta-analysis is the beginning of a study of patients with ovarian cancer aimed not only to the search of therapy with greater anti-tumoral efficacy, but also to research the therapeutic regimen that affects as little as possible in the quality of life of these patients.

For this reason, we should project the interest of new therapies, such as targeted agents.

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