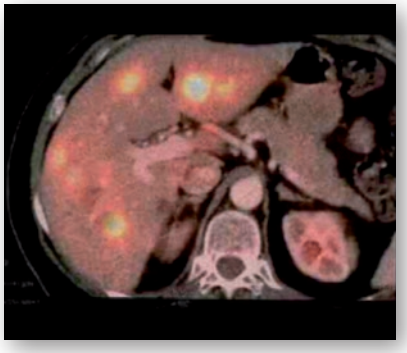

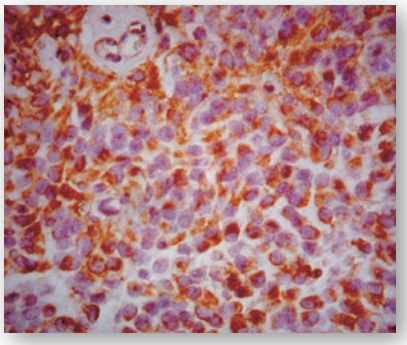

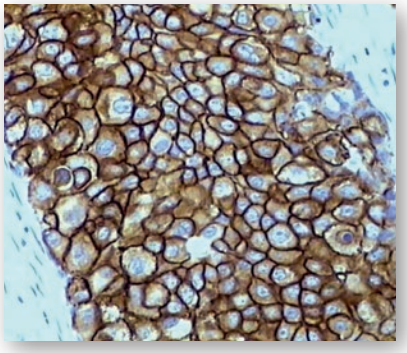

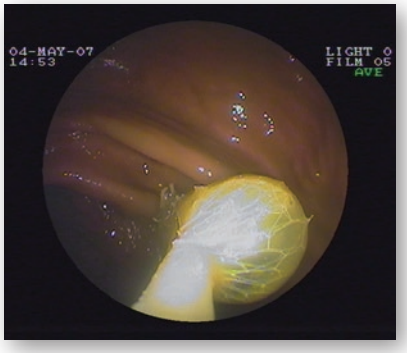

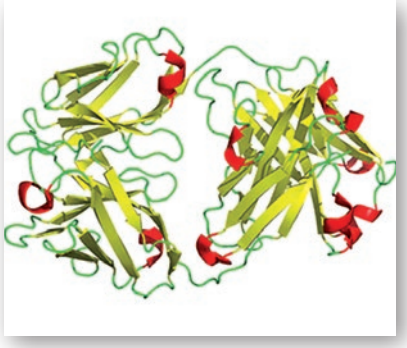

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Clinical management of ovarian cancer aiming to achieve chronic disease

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Introduction

Ovarian cancer is not a rare disease, whose management requires specific expertise. Indeed, clinicians are called onto offer patients treatment solutions suited to each individual case, according to their particular characteristics and phase of the disease. The treatment of recurrence, a stage reached by most patients, is particularly challenging. Although responses are expected in over 80% of women who receive standard platinum-based first-line therapy, the majority of patients with advanced ovarian cancer will ultimately relapse and develop drug-resistant disease[1]. Approximately 20-30% of patients never have a clinical remission and continue to have evidence of residual or progressive disease during treatment. After relapse to first-line treatment, only 10-30% of patients have long-term survival[2]. Therefore, it follows that the increase in survival observed in recent decades has been achieved thanks to improvements in the treatment of recurrence, rather than due to first-line treatments. Furthermore, as most patients experience repeated therapeutic responses and relapses, it is important to design a treatment strategy that includes several lines of therapy, in the correct sequence and from early stages, in an attempt to offer the patient all effective available options.

This volume presents the available evidence regarding the treatment of recurrent ovarian cancer, evaluated by experts in the fields of diagnosis and both medical and surgical therapy. Throughout this review, it is explained how a multidisciplinary approach can allow the development of personalized management strategies based on new knowledge and new resources. Different aspects to be considered in the management of recurrent ovarian cancer such as the importance of planning a correct sequential treatment strategy, the clinical implications of BRCA mutations, and the role of surgery will also be analyzed in depth.

References

1. Markman M, Bookman MA. Second-line treatment of ovarian cancer. Oncologist. 2000;5:26-35.
2. Cannistra SA. Cancer of the ovary. N Engl J Med. 2004;351: 2519-29.

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The multidisciplinary approach in the treatment of ovarian cancer and the importance of the reference center

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In recent decades, new knowledge and the advent of novel diagnostic and therapeutic resources have made the approach to the management of patients with ovarian cancer increasingly complex[1]. Ovarian cancer is biologically heterogeneous, and the sensitivity to treatment varies greatly from case to case[2]. Over the past few decades, the improvements in our understanding of tumors, their biology, diversification, and complexity have allowed modern oncology to deal with a continuous series of new challenges. An ever better understanding of the mechanisms underlying tumor growth and spread has made it possible to develop increasingly sophisticated therapies that specifically target the different neoplastic isotypes. Hence, since the second half of the past century, the two main therapeutic approaches to ovarian cancer (namely, chemotherapy and surgery) have progressed along parallel tracks. In recent years, the need to combine these approaches has changed the outlook regarding the treatment program for cancer patients, which has called for increasingly close interaction between the various players involved in the treatment process (surgeons, oncologists, but also, in certain cases, and radiotherapists). This multidisciplinary approach is essential for the diagnosis and care process, allowing the development of complex treatment protocols combined with a more specific treatment of symptoms (pain therapy and psychological and dietary counseling). The direct consequence of the introduction of these techniques is the need to adapt health-care facilities to meet the new requirements. Disjointed treatment programs are no longer viable for complex and challenging diseases such as ovarian cancer[3,4]. Indeed, the management of ovarian cancer requires ever-greater expertise and increasingly sophisticated equipment that can only be found in specialized facilities, through an interaction between experts from different sectors. In the multidisciplinary management of ovarian cancer, several different professionals must play important roles:

- Radiologists: Imaging techniques such as CT, MRI, and PET allow to pinpoint the disease site and therefore to define the most appropriate intervention and the right timing.
- Pathologists: The histological classification and the definition of the different histopathological variables have a fundamental role to play in the identification of prognostic factors and the selection of the treatment strategy.
- Oncological gynecologists: Surgery is the key element in the management of ovarian cancer; surgical approach requires performing tumor debulking procedures that are not only merely limited to the pelvis but also in the upper abdomen. Oncological gynecologists also play a key role in providing a link between the rest of the professionals involved.
- Medical oncologists: Conventional chemotherapy and the increasing use of novel targeted therapies have led to progressive improvements in survival outcomes.
- Radiotherapists: In certain cases, radiotherapy is used to treat inoperable localized lesions or for palliative purposes in advanced lines of therapy.

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Anesthetists, clinical psychologists, nutritionists, and surgeons of other specialties, such as thoracic surgery, general surgery, urology, and plastic/reconstructive surgery, are other professionals involved in the multidisciplinary management. Importantly, nursing staff also plays a key role, especially in patient management and support[3,4].

Another important aspect in the management of patients with ovarian cancer is the centralization of reference centers. Scientific studies, conducted to assess oncological results at reference centers, have shown that centralizing ovarian cancer patients in specialized facilities can guarantee higher standards of care and better oncological outcomes[5-7].

As early as 1997, the Society of Surgical Oncology (SSO) reached the conclusion that *"Optimal management of ovarian cancer requires the skillful and appropriate integration of cancer surgery and chemotherapy, and is best carried out in centers in which an experienced and coordinated multidisciplinary team is available"*[8], thereby stressing that a multidisciplinary approach and treatment in centralized facilities are of fundamental importance for the management of ovarian cancer. In 2002, the American College of Obstetricians and Gynaecologists published a Committee Opinion that recommends referring patients to an oncological gynecologist in cases in which ovarian cancer is suspected[9]. The surgical aspect particularly demands its performance in a specialized facility, since receiving the best possible surgery is of paramount for the prognosis of ovarian cancer patients. In fact, increasingly robust data reflect the correlation between optimal debulking surgery and improved survival outcomes[10,11]. Several studies have shown that the volume of the center is an independent variable for estimating the likelihood to achieve a complete debulking surgery. A Finnish prospective study showed that a patient with Stage III ovarian cancer treated by an oncological gynecologist at a reference center was 3 times more likely to have radical surgery (without residual disease) than a patient treated by general gynaecologists[12].

In 2015, an American study conducted on 11,865 patients with Stage III/IV ovarian cancer assessed which factors could affect the likelihood of obtaining adequate treatment[10]. It was found that being treated in a non-reference center increased the likelihood of receiving sub-optimum surgery or not receiving surgery at all[10]. Additional studies have also shown that treatment in reference centers increases (5 times) the probability of obtaining a correct surgical staging, an element that has considerable prognostic and therapeutic implications[11].

Survival is one of the most important indicators for assessing the efficacy of a cancer treatment[13]. Several analyses, mostly retrospective, have indicated that the volume of the center correlates with disease-free survival and long-term survival[13-16].

In one of the first studies on this subject, by evaluating the Japanese data of the Osaka Cancer Registry, Ioka et al. showed that receiving surgery in a reference center improves survival in ovarian cancer patients[16]. Similar results were obtained in the study published by Mercado et al., demonstrating that treatment by expert physicians in reference centers is associated with a 40% higher survival than treatment at non-specialized centers[14]. In line with the results of a number of publications, it has been extensively established that receiving surgery from a team of oncological gynecologists leads to better outcomes than when surgery is performed by general surgeons or general gynecologists[13,15].

Another important aspect regarding case centralization is the management of complications associated with treatment (be it surgical, medical, or radiotherapy). Indeed, although patients treated in reference centers have a higher rate of complications (due to the more intensive treatments received), patients treated in low-volume centers have a 50% higher probability of dying from treatment complications[17].

In addition to the adequacy of the facilities and the experience of the medical staff, the improved outcomes of cancer patients treated at reference centers reflect better adherence with standard treatments[7,15]. According to the National Comprehensive Cancer Network (NCCN), the optimum treatment for patients with ovarian cancer consists of preferably optimal debulking surgery (absence of residual disease), followed by six cycles of platinum-based chemotherapy[18]. Receiving treatment that does not comply with guidelines increases the risk of an unfavorable disease course[19]. US data showed that treatment paradigm adherence is significantly better in reference centers[20].

Given the medical literature data that show how treatment in reference centers improves the prognosis of patients with ovarian cancer, patients must be guaranteed treatment programs that allow the centralization of oncological cases in dedicated facilities. Centralization and management by a team of experts with interdisciplinary expertise allow to obtain better oncological outcomes, which reduces inadequate treatments and improves the management of treatment complications.

References

1. Michener CM, Belinson JL. Modern management of recurrent ovarian carcinoma. A systematic approach to a chronic disease. Oncology (Williston Park). 2005;19:1277-85.

2. Chen GM, Kannan L, Geistlinger L, Kofia V, Safikhani Z, Gendoo DMA, et al. Consensus on molecular subtypes of high-grade serous ovarian carcinoma. Clin Cancer Res. 2018;24:5037-47.
3. Heudel PE, Devouassoux-Shisheboran M, Taieb S, Genestie C, Selle F, Morice P, et al. Multidisciplinary management of advanced ovarian cancer for an optimal therapeutic strategy. Eur J Gynaecol Oncol. 2017;38:175-80.
4. Bjørn SF, Schnack TH, Lajer H, Christensen IJ, Lundvall L, Thomsen LN, et al. Classification of ovarian cancer surgery facilitates treatment decisions in a gynecological multidisciplinary team. Int J Gynecol Cancer. 2017;27:382-9.
5. Bonte AS, Luyckx A, Wyckmans L, Trinh XB, van Dam PA. Quality indicators for the management of endometrial, cervical and ovarian cancer. Eur J Surg Oncol. 2019;45:528-37.
6. Carter J, Pather S, Nascimento M. Current status of ovarian cancer surgical management. Argument for centralisation of care in Australia. Aust N Z J Obstet Gynaecol. 2018;58:474-7.
7. Escayola C, Torrent JJ, Ferron G, Quenet F, Querleu D. When and who should perform epithelial ovarian cancer surgery? Int J Gynecol Cancer. 2018;28:594-9.
8. Hoskins W, Rice L, Rubin S. Ovarian cancer surgical practice guidelines. Society of surgical oncology practice guidelines. Oncology (Williston Park). 1997;11:896-900, 903-4.
9. American College of Obstetricians anf Gynecologists. ACOG Committee Opinion: number 280, December 2002. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. Obstet Gynecol. 2002;100:1413-6.
10. Long B, Chang J, Ziogas A, Tewari KS, Anton-Culver H, Bristow RE. Impact of race, socioeconomic status, and the health care system on the treatment of advanced-stage ovarian cancer in California. Am J Obstet Gynecol. 2015;212:468.e1-9.
11. Vernooij F, Heintz AP, Coebergh JW, Massuger LF, Witteveen PO, van der Graaf Y. Specialized and high-volume care leads to better outcomes of ovarian cancer treatment in the Netherlands. Gynecol Oncol. 2009;112:455-61.
12. Kumpulainen S, Kuoppala T, Leminen A, Penttinen J, Puistola U, Pukkala E, et al. Surgical treatment of ovarian cancer in different hospital categories--a prospective nation-wide study in Finland. Eur J Cancer. 2006;42:388-95.
13. Bristow RE, Chang J, Ziogas A, Randall LM, Anton-Culver H. High-volume ovarian cancer care: survival impact and disparities in access for advanced-stage disease. Gynecol Oncol. 2014;132:403-10.
14. Mercado C, Zingmond D, Karlan BY, Sekaris E, Gross J, Maggard-Gibbons M, et al. Quality of care in advanced ovarian cancer: the importance of provider specialty. Gynecol Oncol. 2010; 117:18-22.
15. Bristow RE, Chang J, Ziogas A, Campos B, Chavez LR, Anton-Culver H. Impact of national cancer institute comprehensive cancer centers on ovarian cancer treatment and survival. J Am Coll Surg. 2015;220:940-50.
16. Ioka A, Tsukuma H, Ajiki W, Oshima A. Influence of hospital procedure volume on ovarian cancer survival in Japan, a country with low incidence of ovarian cancer. Cancer Sci. 2004;95:233-7.
17. Wright JD, Herzog TJ, Siddiq Z, Arend R, Neugut AI, Burke WM, et al. Failure to rescue as a source of variation in hospital mortality for ovarian cancer. J Clin Oncol. 2012;30:3976-82.
18. Morgan RJ Jr., Alvarez RD, Armstrong DK, Boston B, Burger RA, Chen LM, et al. Epithelial ovarian cancer. J Natl Compr Canc Netw. 2011;9:82-113.
19. Phippen NT, Barnett JC, Lowery WJ, Miller CR, Leath CA 3rd. Surgical outcomes and national comprehensive cancer network compliance in advanced ovarian cancer surgery in a low volume military treatment facility. Gynecol Oncol. 2013;131:158-62.
20. Bristow RE, Chang J, Ziogas A, Anton-Culver H. Adherence to treatment guidelines for ovarian cancer as a measure of quality care. Obstet Gynecol. 2013;121:1226-34.

The role of surgery in the treatment of recurrent ovarian cancer

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Surgery is one of the standard approaches in the management of ovarian cancer at early stages, and it also plays a role in the treatment of recurrence, although this role has not yet been clearly defined. The research conducted in this area focuses on achievable objectives, the identification of candidate patients, and the possibility to affect prognosis.

The fifth Gynecologic Cancer InterGroup consensus conference on ovarian cancer has recently defined the criteria to identify patient subgroups, considering current therapeutic advances and the evidence accumulated in the past decades[1].

The historical definition based on the progression-free interval (PFI) used to define platinum-sensitive/resistant disease has been replaced by the therapy-free interval (TFI) concept. The TFI can be broken down into the platinum therapy-free interval (TFIp), non-platinum therapy-free interval (TFInp), and biological therapy-free interval (TFIb). Other criteria to consider include histology, BRCA mutation status, the number and type of previous treatments, the results of prior therapy, and patient-reported symptoms[1].

Although chemotherapy with targeted therapy clearly forms the basis of recurrent ovarian cancer treatment, the nature of the follow-up and the role of surgery have not yet been established. An unanswered question refers to the criteria that must be met to begin the treatment of recurrent ovarian cancer. Should the diagnosis of recurrence be based on CA-125 levels rather than waiting for the onset of symptoms? Could the anticipation of the diagnosis provide clinical benefit and mark the point at which to start the treatment?

A meta-analysis based on a systematic literature review, including 2,019 patients with recurrent ovarian cancer was conducted. An independent correlation was identified between the percentage of patients undergoing complete debulking surgery and the post-recurrence survival (a 3-month increase in the median survival for each 10% increase in the percentage of patients operated) (Fig. 1)[2].

From a surgical standpoint, the site of recurrence is a key factor. Importantly, just one-third of cases have a single site at the time of the procedure. A retrospective analysis was conducted on 73 patients with isolated lymph node recurrence[3]. Following secondary debulking surgery, at 50-month follow-up, 43.8% of patients were alive and disease-free, 24.6% were alive with disease, and 31.5% had died of ovarian cancer. No significant post-operative morbidity was observed. The authors concluded that, in this type of recurrence, surgical treatment is feasible, tolerated, and associated with good clinical outcomes[3].

With the objective of identifying the characteristic is of patients who could benefit from surgery in the presence of recurrence, a retrospective analysis was conducted on 267 patients who received surgery in different centers in 2006 (DESKTOP I study)[4]. Complete resection was associated with significantly longer survival compared with surgery leaving any post-operative residuals (median 45.2 vs. 19.7 months; HR: 3.71; 95% CI: 2.27-6.05; $p < 0.0001$). Factors associated with complete resection were good performance status, complete resection at first surgery, and absence of ascites. A score for the prediction of complete cytoreduction in recurrent ovarian cancer was proposed based on these factors (AGO score)[4]. DESKTOP II trial was performed to verify this score prospectively[5]. A total of 516 patients with recurrent ovarian

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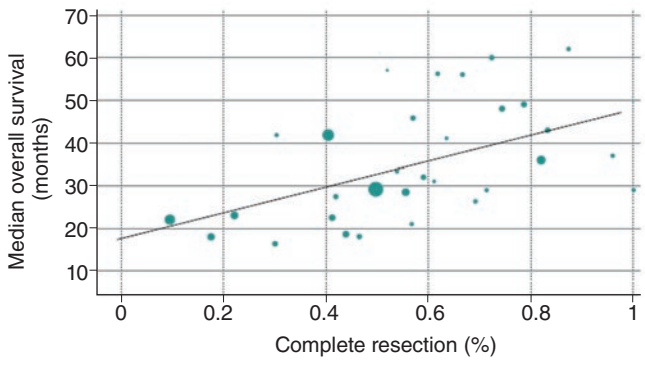

Figure 1. *Correlation between post-recurrence median survival and percentage of patients undergoing complete debulking surgery* (modified from Bristow, et al.[2]).

cancer were enrolled; of these, 261 (51%) were classified as score positive, and 129 patients with a positive score and first relapse were operated on. The rate of complete resection was 76%, thus confirming the validity of this score regarding the positive prediction of complete resectability in two or more of three patients[5].

On the basis of these results, DESKTOP III trial was conducted to investigate the role of secondary cytoreductive surgery in platinum-sensitive ovarian cancer patients with a positive AGO score (PS ECOG 0, ascites ≤ 500 ml, and complete resection at initial surgery)[6].

The ad interim results are available. A total of 407 patients were randomized to second-line chemotherapy or debulking surgery, followed by chemotherapy. Complete resection was achieved in 67% of patients. Median PFS was 19.6 months with surgery and 14 months without surgery (HR: 0.66, 95% CI: 0.52-0.83, p < 0.001). The median time to start of first subsequent therapy (TFST) was 21 versus 13.9 months in favor of the surgery arm (HR: 0.61, 95% CI: 0.48-0.77, p < 0.001) (Fig. 2)[6].

Analysis of the primary endpoint OS is kept blinded due to immaturity and will be evaluated after extended follow-up. The authors concluded that until final OS data will definitively define the role of secondary cytoreductive surgery, it should at least be considered as a valuable option in patients with a positive AGO-Score[6]. Since the advantages of surgery were associated only with complete resection, adequate patient selection should be accompanied by the selection of appropriate centers, which have the necessary facilities and a team of professionals capable of achieving complete resections in the greatest number of possible cases.

Research on tertiary debulking surgery is very limited. Certain authors have evaluated the impact on survival and attempted to identify factors predictive of optimum tertiary resection. Surgery was defined as optimum when the residual disease was 0 or ≤ 0.5 cm[7-9], and the criteria considered to be predictive of a favorable result were tumor size < 5 cm[7], single tumor site[8], and the absence of middle abdominal involvement, i.e., absence of peritoneal carcinomatosis[9]. A multicenter study on the impact of tertiary debulking surgery on survival was published in 2017[10]. The study included 103 patients with recurrent ovarian cancer and a TFI of more than 6 months. Complete debulking was achieved in 71 subjects (68.9%) and was seen to be the best predictive factor of survival. Median OS was 43 months compared to 33 months for patients with residual tumor (p < 0.001). After multivariate adjustment, the presence of a single lesion and good (ECOG 0) performance status was the only significant predictors of complete surgical cytoreduction[10].

Recommendations from the recent ESMO-ESGO consensus conference on ovarian cancer[11] indicate that currently, the option of secondary cytoreductive surgery followed by platinum-based combination therapy should be discussed with all eligible patients. Patients should be selected if they have a high probability of having a complete resection, and the following predictors for resection should be considered:

- Platinum treatment-free interval (TFI) of > 6 months.
- Positive AGO score.

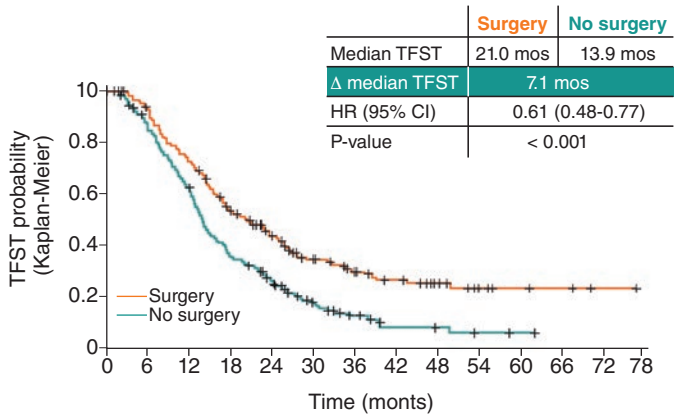

Figure 2. *Ago Desktop III: TFST* (modified from Bois, et al.[6]).

- Absence of probably irresectable lesions on imaging.
- Absence of contraindications to surgery (e.g., comorbidities, and prior severe complications of surgery).

Experts also stand out that centers offering secondary surgeries should have the necessary resources and infrastructures including an established multidisciplinary team coordinating the pre-, intra-, and post-operative care needed to achieve complete resection in the majority of these procedures. Regarding the benefits of tertiary complete cytoreductive surgery, recommendations only mention the limited evidence that currently there is[11].

Considering the newly generated clinical evidence, it is expected that the inclusion of surgery in treatment strategies, based on an appropriate selection of patients, can open perspectives to improve survival.

References

1. Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM, et al. Fifth ovarian cancer consensus conference of the gynecologic cancer intergroup: recurrent disease. Ann Oncol. 2017;28:727-32.
2. Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. Gynecol Oncol. 2009;112:265-74.
3. Ferrero A, Ditto A, Giorda G, Gadducci A, Greggi S, Daniele A, et al. Secondary cytoreductive surgery for isolated lymph node recurrence of epithelial ovarian cancer: a multicenter study. Eur J Surg Oncol. 2014;40:891-8.
4. Harter P, du Bois A, Hahmann M, Hasenburg A, Burges A, Loibl S, et al. Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) desktop ovar trial. Ann Surg Oncol. 2006;13:1702-10.
5. Harter P, Sehouli J, Reuss A, Hasenburg A, Scambia G, Cibula D, et al. Prospective validation study of a predictive score for operability of recurrent ovarian cancer: the multicenter intergroup study DESKTOP II. A project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO. Int J Gynecol Cancer. 2011;21:289-95.
6. du Bois A, Vergote I, Ferron G, Reuss A, Meier W, Greggi S, et al. Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20. J Clin Onco. 2017;35 Suppl 15:5501.
7. Karam AK, Santillan A, Bristow RE, Giuntoli R 2nd, Gardner GJ, Cass I, et al. Tertiary cytoreductive surgery in recurrent ovarian cancer: selection criteria and survival outcome. Gynecol Oncol. 2007;104:377-80.
8. Shih KK, Chi DS. Maximal cytoreductive effort in epithelial ovarian cancer surgery. J Gynecol Oncol. 2010;21:75-80.
9. Fotopoulou C, Richter R, Braicu IE, Schmidt SC, Neuhaus P, Lichtenegger W, et al. Clinical outcome of tertiary surgical cytoreduction in patients with recurrent epithelial ovarian cancer. Ann Surg Oncol. 2011;18:49-57.
10. Falcone F, Scambia G, Benedetti Panici P, Signorelli M, Cormio G, Giorda G, et al. Tertiary cytoreductive surgery in recurrent epithelial ovarian cancer: a multicentre MITO retrospective study. Gynecol Oncol. 2017;147:66-72.
11. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol. 2019;30:672-705.

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The importance of planning a correct therapeutic strategy in patients with recurrent ovarian cancer

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Diagnosing a recurrence is a very delicate moment in the management of ovarian cancer as, from a prognostic point of view; the patient is unlikely to be cured. From that point, the effort to be made must employ available medical and surgical options to achieve chronic disease status, prolonging patient's survival with the best possible quality of life. The right approach is by planning, whenever possible, a sequential treatment strategy allowing the use of all the treatment options currently available.

As the general objective for patients with recurrent ovarian cancer is non-curative, tolerability is of great importance for treatment selection. Consequently, the best time to start treating the patient must be carefully evaluated, taking into account the fact that each therapy is accompanied by a risk of adverse events that may have an impact on the quality of life[1]. Concerning the criteria that indicate recurrence, there is no consensus on the management of ovarian cancer patients who, following complete clinical response to first-line therapy, have increased CA-125 levels in the absence of symptoms of recurrence[2]. In the MRC OV05/EORTC 55955 study, Rustin et al.[3] suggested that reintroducing chemotherapy at this stage does not improve survival and that, therefore, the value of routine measurement of CA-125 in the follow-up of patients with ovarian cancer who attain a complete response after first-line treatment is not proven[3]. The National Comprehensive Cancer Network (NCCN) 2016 guidelines[4] suggest different options to be considered: waiting for clinical recurrence, enrolling the patient in a clinical study, or even starting second-line therapy with an agent with an acceptable tolerability profile.

With regard to the selection of treatment and especially, to the design of the sequential strategy for the different lines of therapy, different factors should be taken into consideration, such as:

- Histology.
- Genetic mutations.
- Characteristics of the recurrence (site, resectability, and presence of symptoms).
- Prior therapies.
- Number of lines of treatment.
- Patient's general condition.
- Treatment-free interval (TFI), which since the arrival of targeted therapies, has been broken down into:
  - Platinum-free interval (PFI).
  - Non-platinum TFI.

Although the PFI is no longer the only factor to be considered for treatment selection, it remains of considerable importance. Conventionally, patients have been classified into different groups according to the PFI after platinum-based first-line therapy. Refractory patients are those who relapse during platinum-based chemotherapy or within 4 weeks of treatment; resistant patients experience recurrence within 6 months after the end of therapy; partially-sensitive patients relapse between 6 and 12 months and those that are fully sensitive experience recurrence more than 12 months from the end of chemotherapy. These patient segments have different prognoses, with different response

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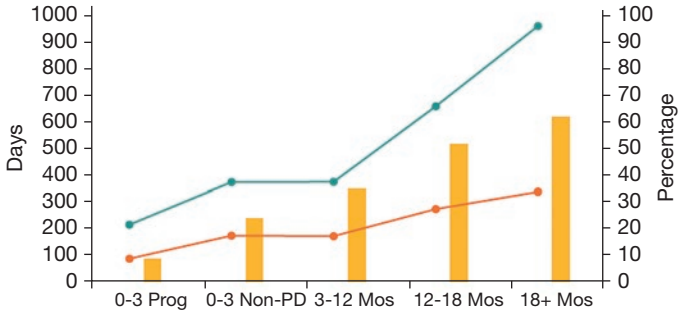

PFS, days	90	176	174	275	339
OS, days	217	375	375	657	957
Response, %	9	24	35	52	62

Figure 1. *Progression-free interval and treatment efficacy* (modified from Pujade-Lauraine, et al.[5]).

rates and survival outcomes (Fig. 1). However, platinum sensitivity is a continuous variable, so it is difficult in any case to characterize patients based on defined time intervals[5].

The different prognoses of the previous patients' populations entail large variations in the treatment objective[6]. For patients with a poor prognosis (classified as refractory or resistant to platinum), the aim of treatment consists of controlling symptoms and maintaining the quality of life.

The case is very different when patients have a better prognosis (platinum-sensitive patients), for whom the goal of therapy is to increase progression-free survival (PFS) to each line of therapy, allowing a possible survival extension and leading to disease chronification. At the expense of incorporating recent findings on the use of PARP inhibitors (PARPi) in the first-line setting[7-10], the current recommendation of the scientific community is to use platinum with or without bevacizumab or a PARPi in all those patients for whom platinum re-treatment might be the best option[11]. However, there are situations in which platinum rechallenge is not the best option, even for ovarian cancer patients considered sensitive to platinum. The main limitations of platinum re-treatment are the increased toxicity and the decreased efficacy usually observed after each new re-exposure to platinum[12]. Importantly, the consensus has not been reached regarding the best treatment option to be offered to patients with limited sensitivity to platinum (recurrence between 6 and 12 months)[12-14]. Issues that may prevent platinum rechallenge are especially relevant for these patients (Table 1), since, after platinum-based first-line therapy, the response rate to subsequent platinum is significantly low (27-33%), with a TTP inferior to 6 months[12].

The aim of treatment for patients with limited sensitivity to platinum includes an improvement in the time to progression (TTP) and in OS. In the OVA-301 study, when this subgroup of patients received platinum as subgroup of patients therapy[15], TTP was extended in 4 months with trabectedin + PLD versus PLD monotherapy (median TTP 11.5 vs. 7.5 months, respectively; HR = 0.61; p = 0.0203) (Fig. 2). Regarding survival, treatment with trabectedin + PLD in this subset of patients resulted in a significant 9-month improvement in median OS compared with PLD (27.7 vs. 18.7 months; HR: 0.58; p = 0.0153)[16].

A further analysis was performed to better understand the impact of adding trabectedin to PLD in the outcomes of post-progression therapy. Survival was accounted from the moment of administration of subsequent platinum after completion of the OVA-301 trial. Median OS with platinum was significantly extended by 8.7 months (18.6 vs. 9.9 months; HR = 0.54; p = 0.0169) when patients received trabectedin + PLD instead of PLD monotherapy in the previous line (Fig. 2)[15].

These observations are in line with trabectedin's mechanism of action, as this agent may restore tumor sensitivity to platinum by modifying the tumor microenvironment and by selecting cancer cells that are more responsive to platinum[12]. Based on the clinical evidence, trabectedin + PLD represents a valuable treatment for platinum-sensitive patients for whom platinum rechallenge might not be the best option, such as patients with limited sensitivity to platinum.

Table 1. *Treatment options and expectations for patients with recurrent ovarian cancer and limited sensitivity to platinum*

Treatment options	What effects to expect?
Re-treatment with platinum (carboplatin + taxane/ gemcitabine/PLD ± maintenance therapy)	– Demonstrated efficacy in phase 3 clinical trials; efficacy decreases after each new line of treatment (in clinical practice) – Cumulative increase in toxicity
Combination without platinum (trabectedin + PLD)	– Potential improvement in the response to subsequent treatment with platinum and prolongation of survival – Time to recover from the toxicity caused by previous treatments while taking an active agent – Only option in patients who are not eligible for another platinum-based therapy
Monotherapy without platinum (e.g., PLD)	– Efficacy poorer than the previous treatment options (MITO-8 and OVA-301 studies) – Adequate safety profile

PLD: pegylated liposomal doxorubicin.
Modified from Colombo[12].

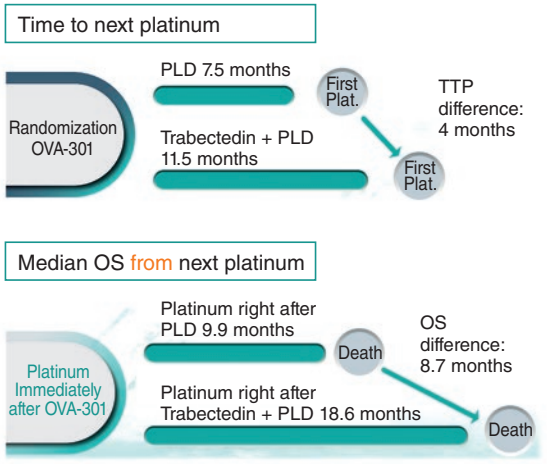

Figure 2. *Outcomes in the patient subgroup from the OVA-301 study with a PFI of 6-12 months who received platinum-based chemotherapy after treatment with trabectedin + PLD or PLD alone* (modified from Colombo[12]).

As previously mentioned, other factors such as prior therapies and the number of lines should be considered when planning the treatment sequence for attempting to achieve chronic disease status. The ever-greater use of platinum is leading to an increase of hypersensitivity cases. The incidence of hypersensitivity reactions to carboplatin gradually increases with the number of cycles. From only 1% of hypersensitivity reactions observed during the first five cycles of platinum, it increases to 27% beyond the seventh cycle and reaches 44% when platinum is administered in the third line[17]. In these situations, or to prevent them, the introduction of an effective non-platinum-based therapy allows treatment continuation avoiding the onset of hypersensitivity reactions or cumulative and irreversible platinum-associated toxicities such as severe myelosuppression, ototoxicity, or renal toxicity[18]. Trabectedin+PLD combination has also shown relevant results in platinum-sensitive ovarian cancer, being in line with other treatment options available for these patients[19] (Fig. 3) and representing the

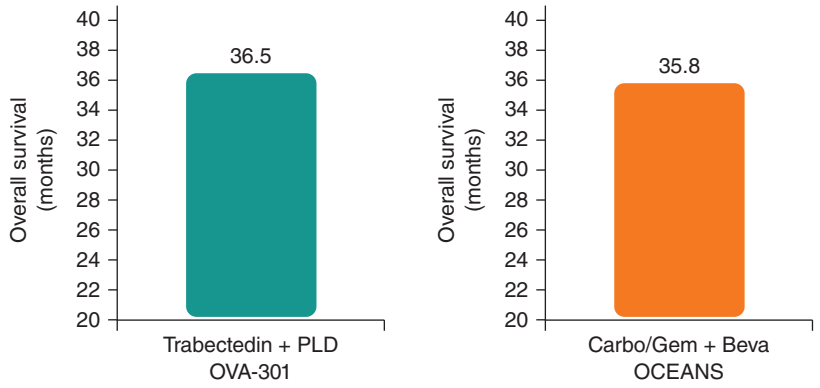

Figure 3. *OS data in patients with a PFI > 12 months obtained in the OVA-301 and OCEANS trials* (modified from González[19]).

alternative for patients not eligible to platinum despite being considered sensitive.

Genetic mutations are another key factor to be taken into consideration when planning the treatment strategy. BRCA1 and BRCA2 gene mutations increase the predisposition to the development of ovarian cancer and are observed in 14% of diagnosed tumours[20]. BRCA1 and BRCA2 encode proteins that play an essential role in the double-stranded DNA break repair mechanisms by homologous recombination (HR). The loss of function of the BRCA1/2 proteins due to the effect of constitutional or somatic mutations of the corresponding genes is the most common, but not the only, dysfunction of HR mechanisms[21,22].

The presence of BRCA mutation is associated with better prognosis, response to various types of chemotherapy and increased treatment-related toxicities. Indeed, this mutation and low expression of the BRCA protein are associated with increased cell sensitivity to ionizing radiation and to the DNA damage caused by cytostatic agents[23]. Retrospective studies have demonstrated that ovarian cancer patients with a BRCA germline mutation have a greater pharmacological sensitivity to therapeutic combinations containing platinum derivatives[24-26], as well as greater sensitivity to trabectedin and PLD[27,28]. It has also been demonstrated that the pathogenetic variants of the BRCA genes, be they germline or somatic, constitute a biomarker of greater sensitivity to treatment with inhibitors of the PARP enzyme, which intervenes in the repair of single-strand DNA breaks. According to clinical evidence collected to date in this setting, it is recommended to perform the BRCA test at the time of the initial diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer[29]. An early detection of BRCA mutations helps to organize and plan correct therapeutic strategy, allowing the implementation of an optimal personalized therapy.

Patients with BRCA mutation benefit more from chemotherapy not only in terms of palliation but also in terms of survival[30], and therefore receive a greater number of lines of therapy. The best prognosis of these patients implies an even greater relevance of the proper sequential management of the disease, being key the use of all available medications. Trabectedin + PLD combination is a treatment option for these patients, who often relapse between 6 and 12 months after several lines of platinum. As part of the Phase III study OVA-301[31], an exploratory analysis was conducted to evaluate whether an impairment of the BRCA mutation-related HR mechanism could affect the efficacy of trabectedin + PLD versus single-agent PLD[32]. Forty-one out of 264 (16%) study participants were BRCA-mutated; of them, 17 received trabectedin + PLD and 24 received PLD monotherapy. Treatment with the combination was associated with longer PFS (median 13.5 vs. 5.5 months; p = 0.0002) and longer OS (median 23.8 vs. 12.5 months; p = 0.0086) (Fig. 4)[32]. Therefore, trabectedin + PLD proved to be particularly efficacious on cells lacking HR repair mechanisms.

Debulking surgery also affects the time of recurrence. In advanced ovarian cancer patients with diffuse peritoneal carcinomatosis, time to recurrence was longer after primary complete debulking

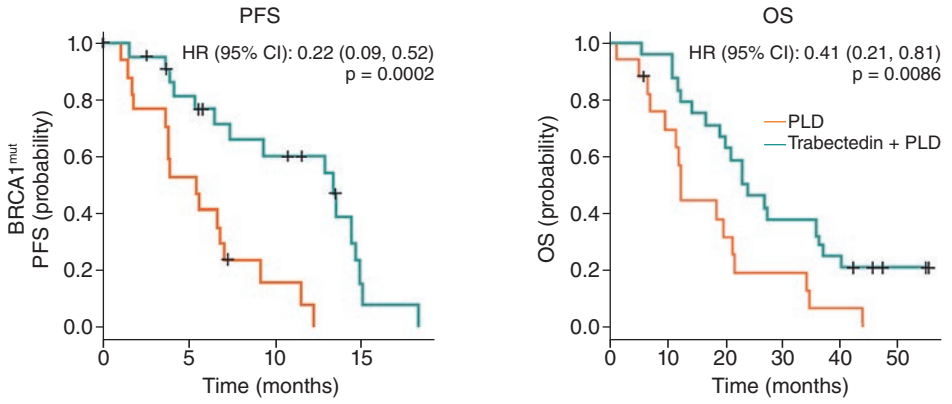

Figure 4. *PFS and OS in patients with BRCA mutations treated with trabectedin + PLD or PLD alone* (modified from Monk, et al.[32]).

surgery than after administering neoadjuvant chemotherapy followed by interval surgery without residual tumor[33]. The DESKTOP study showed that complete surgery alone was associated with longer survival in patients with ovarian cancer[34].

Finally, the choice of treatment strategy must also take into account the patient's expectations and wishes (e.g., therapies that do not cause hair loss) as well as the logistical and economic factors that may affect the selection of the treatment.

References

1. Markman M, Bookman MA. Second-line treatment of ovarian cancer. Oncologist. 2000;5:26-35.
2. Wang F, Ye Y, Xu X, Zhou X, Wang J, Chen X. CA-125-indicated asymptomatic relapse confers survival benefit to ovarian cancer patients who underwent secondary cytoreduction surgery. J Ovarian Res. 2013;6:14.
3. Rustin GJ, van der Burg ME, Griffin CL, Guthrie D, Lamont A, Jayson GC, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet. 2010;376:1155-63.
4. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer Version 1; 2016. Available from: https://www.nccn.org.
5. Pujade-Lauraine E, Largillier R, Weber B, Gladieff L, Alexandre J, Durando X, et al. Predicting the effectiveness of chemotherapy (Cx) in patients with recurrent ovarian cancer (ROC): A GINECO study. Proc Am Soc Clin Oncol. 2002;21:208a.
6. Pisano C, Bruni GS, Facchini G, Marchetti C, Pignata S. Treatment of recurrent epithelial ovarian cancer. Ther Clin Risk Manag. 2009;5:421-6.
7. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018; 379:2495-505.
8. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019; 381:2391-402.
9. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019; 381:2403-15.
10. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Sevelda P, et al. Phase III PAOLA-1/ENGOT-ov25 trial: olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer (OC) treated with platinum-based chemotherapy (PCh) plus bev. Ann Oncol. 2019;30 Suppl 5:v851-934.
11. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. Ann Oncol. 2019;30:672-705.
12. Colombo N. Recurrent ovarian cancer 8 months after induction and bevacizumab consolidation: rationale for using trabectedin + pegylated liposomal doxorubicin in second line. Expert Rev Anticancer Ther. 2018;18:13-7.
13. Colombo N, Gore M. Treatment of recurrent ovarian cancer relapsing 6-12 months post platinum-based chemotherapy. Crit Rev Oncol Hematol. 2007;64:129-38.
14. Poveda A, Ray-Coquard I, Romero I, Lopez-Guerrero JA, Colombo N. Emerging treatment strategies in recurrent platinum-sensitive ovarian cancer: focus on trabectedin. Cancer Treat Rev. 2014;40:366-75.
15. Kaye SB, Colombo N, Monk BJ, Tjulandin S, Kong B, Roy M, et al. Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer delays third-line chemotherapy and prolongs the platinum-free interval. Ann Oncol. 2011;22:49-58.
16. Colombo N. Optimizing treatment of the partially platinum-sensitive ovarian cancer patient. Future Oncol. 2013;9(12 Suppl. 1):19-23.
17. Makrilia N, Syrigou E, Kaklamanos I, Manolopoulos L, Saif MW. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. Met Based Drugs. 2010;2010:207084.
18. Fotopoulou C. Limitations to the use of carboplatin-based therapy in advanced ovarian cancer. EJC Suppl. 2014;12:13-6.
19. González A. Increasing the chances for platinum-sensitive ovarian cancer patients. Future Oncol. 2013;9:29-35.
20. Gadducci A, Guarneri V, Peccatori FA, Ronzino G, Scandurra G, Zamagni C, et al. Current strategies for the targeted treatment of high-grade serous epithelial ovarian cancer and relevance of BRCA mutational status. J Ovarian Res. 2019;12:9.
21. Curtin NJ. DNA repair dysregulation from cancer driver to therapeutic target. Nat Rev Cancer. 2012;12:801-17.
22. Hilton JL, Geisler JP, Rathe JA, Hattermann-Zogg MA, DeYoung B, Buller RE. Inactivation of BRCA1 and BRCA2 in ovarian cancer. J Natl Cancer Inst. 2002;94:1396-406.

23. Huszno J, Budryk M, Kołosza Z, Nowara E. The influence of BRCA1/BRCA2 mutations on toxicity related to chemotherapy and radiotherapy in early breast cancer patients. Oncology. 2013; 85:278-82.
24. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian ovarian cancer study group. J Clin Oncol. 2012;30:2654-63.
25. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA. 2012;307:382-90.
26. George A, Kristeleit R, Rafii S, Michie CO, Bowen R, Michalarea V, et al. Clinical factors of response in patients with advanced ovarian cancer participating in early phase clinical trials. Eur J Cancer. 2017;76:52-9.
27. Safra T, Borgato L, Nicoletto MO, Rolnitzky L, Pelles-Avraham S, Geva R, et al. BRCA mutation status and determinant of outcome in women with recurrent epithelial ovarian cancer treated with pegylated liposomal doxorubicin. Mol Cancer Ther. 2011;10:2000-7.
28. Monk BJ, Lorusso D, Italiano A, Kaye SB, Aracil M, Tanović A, et al. Trabectedin as a chemotherapy option for patients with BRCA deficiency. Cancer Treat Rev. 2016;50:175-82.
29. Linee guida AIOM. Tumori Dell'ovaio; 2018.
30. Zhong Q, Peng HL, Zhao X, Zhang L, Hwang WT. Effects of BRCA1- and BRCA2-related mutations on ovarian and breast cancer survival: a meta-analysis. Clin Cancer Res. 2015;21: 211-20.
31. Monk BJ, Herzog TJ, Kaye SB, Krasner CN, Vermorken JB, Muggia FM, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol. 2010;28: 3107-14.
32. Monk BJ, Ghatage P, Parekh T, Henitz E, Knoblauch R, Matos-Pita AS, et al. Effect of BRCA1 and XPG mutations on treatment response to trabectedin and pegylated liposomal doxorubicin in patients with advanced ovarian cancer: exploratory analysis of the phase 3 OVA-301 study. Ann Oncol. 2015; 26:914-20.
33. Petrillo M, Ferrandina G, Fagotti A, Vizzielli G, Margariti PA, Pedone AL, et al. Timing and pattern of recurrence in ovarian cancer patients with high tumor dissemination treated with primary debulking surgery versus neoadjuvant chemotherapy. Ann Surg Oncol. 2013;20:3955-60.
34. Harter P, du Bois A, Hahmann M, Hasenburg A, Burges A, Loibl S, et al. Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) desktop ovar trial. Ann Surg Oncol. 2006;13:1702-10.

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Current treatment strategies for an optimum management of chronic disease

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Ovarian cancer has a particular clinical history, involving a very high response rate to first-line therapy, followed by a relapse in over 80% of patients and continuing with repeated remissions and relapses. In the design of the treatment strategy both at first diagnosis and at recurrence, it is important to consider that ovarian cancer is a heterogeneous disease that involves different histotypes (high-grade serous [70%], low-grade serous [4%], mucinous [8%], endometrioid [8%], and clear cell [10%]) with different biological and molecular characteristics[1]. This heterogeneity leads to different prognosis and different sensitivity to available therapies, suggesting the application of diversified treatment strategies.

The standard first-line therapy consists of chemotherapy with carboplatin and paclitaxel after debulking surgery[1]. The addition of bevacizumab as maintenance therapy has shown to improve PFS in patients with Stage III-IV ovarian cancer[2]. However, uncertainties persist as to how bevacizumab should be used, specifically with regard to the identification of candidate patients, molecular markers, doses, duration, and retreatment.

For patients who have responded to first-line chemotherapy, maintenance or consolidation therapy could delay recurrence or even, for the first time, favor the disease's eradication. Indeed, recent studies have opened up a number of perspectives in this direction. To date, decidedly important results have been achieved with poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi) in the SOLO 1 study[3], in which olaparib showed, in patients with BRCA mutation who obtained complete or partial response with platinum-based first-line therapy, a 70% reduction in the risk of progression or death compared to placebo. Of the patients treated with olaparib, 60.4% remained progression-free after 36 months, compared to 26.9% of women in the placebo arm.

Recent studies have tested PARPi maintenance after a complete or partial response to first-line platinum without being limited to BRCA mutated patients:

- In the PRIMA study, maintenance with niraparib compared to placebo resulted in a median PFS of 13.8 months versus 8.2 months (hazard ratio [HR], 0.62; $p < 0.001$) in the overall population and in 21.9 months versus 10.4 months (HR, 0.43; $p < 0.001$) in patients with homologous recombination deficiency (HRD)[4].
- In the intention-to-treat (ITT) population of the PAOLA-1 study, there was a statistically significant improvement in PFS when olaparib compared with placebo was added to first-line standard-of-care bevacizumab maintenance treatment. Median PFS was 22.1 months versus 16.6 months, respectively (HR, 0.59; $p < 0.001$). In patients with HRD, the difference in the median PFS almost reached 20 months (37.2 vs. 17.7 months; HR, 0.33)[5].

A third study tested the maintenance with PARPi in patients with previously untreated ovarian cancer without doing any previous selection of patients responding to platinum-based therapy:

- Maintenance with veliparib was compared to placebo in the VELIA study. Median PFS was 23.5 months versus 17.3 months (HR, 0.68; $p < 0.001$) in the ITT population. The hazard ratio value decreased to 0.57 in the HRD population[6].

Once these first-line treatment options have been granted marketing authorization by regulatory authorities, new treatment algorithms incorporating

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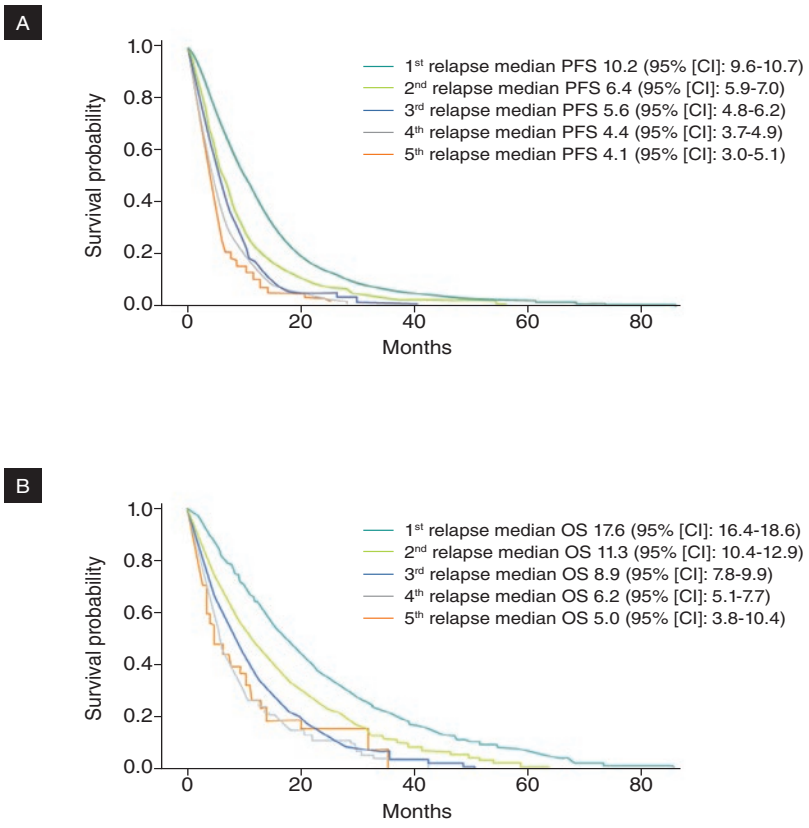

Figure 1. *Kaplan–Meier analyses PFS and OS were carried out in the whole patients' cohort depending on subsequent relapse.* ***A:*** *shows PFS after relapse 1-5.* ***B:*** *shows OS after relapse 1-5* (modified from Hanker, et al.[7]).

the novel options of PARPi and bevacizumab use should be agreed.

As mentioned previously, the systemic treatment of recurrent ovarian cancer is rarely curative. Treatment objectives of advanced lines are to prolong the next relapse and survival, control the progression of symptoms and improve patients' quality of life, thereby achieving chronic disease status. The chronification of recurrent ovarian cancer is intimately linked with administering active drugs at each new relapse, even to patients who are in very advanced lines. A characterization of advanced lines of therapy and its effects on survival was carried out based on data of 1,620 ovarian cancer patients[7]. Relapse treatment improved PFS and OS also in very advanced lines. Both in third- and fourth-line therapy, there was a PFS gain of 3.5 months for patients receiving relapse treatment compared with patients without any treatment (Fig. 1A). Furthermore, there was a significant OS gain in the third-, fourth-, and fifth-line treatment of 10.1, 7.3, and 4.3 months, respectively (Fig. 1B). These data indicate that multiple lines of treatment can be effective and should, therefore, be considered.

Today there are various treatment options for advanced lines. The duration of the platinum-free interval (PFI) has traditionally guided the treatment selection of ovarian cancer recurrences. However, conclusions from the recent ESGO-ESMO Consensus Conference on Ovarian Cancer[8] recommend to avoid the traditional classification made in terms of exact timing of recurrence. The new definition of platinum resistance includes when progression occurs during therapy with platinum (proven resistance) or when there is an early recurrence of symptoms with a low probability of response to platinum (presumed/expected resistance). The low probability of response to platinum is precisely the characteristic of patients in the grey area, traditionally defined as partially platinum-sensitive/resistant patients (those with limited sensitivity to platinum,

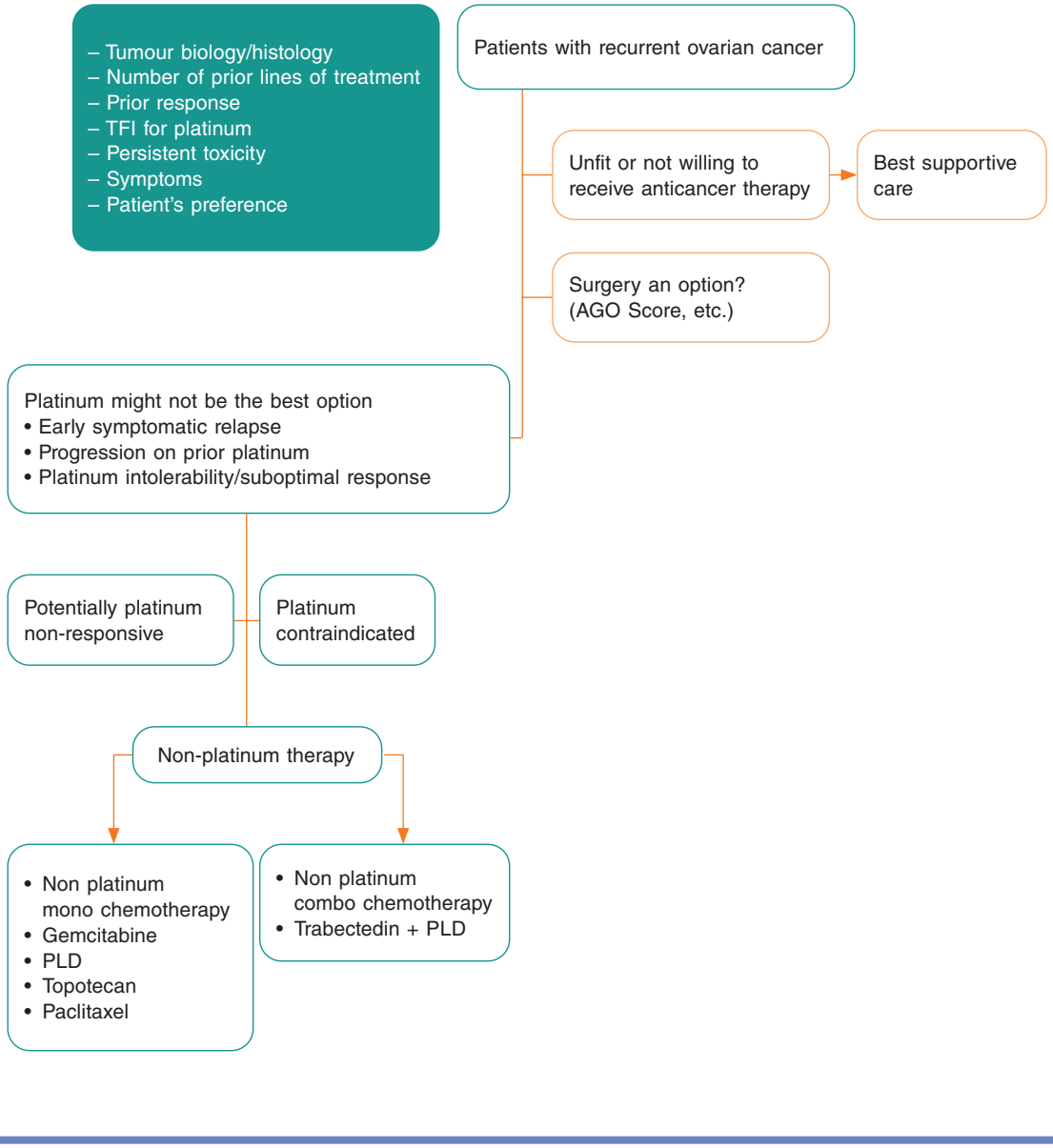

Figure 2. *Decision-making algorithm for the treatment of recurrent ovarian cancer when platinum is not the best option* (modified from Colombo, et al.[8]).

relapsing between 6 and 12 months). The traditional classification based on the temporal assessment of the recurrence will have to be adapted to suit the new approach suggested by the consensus. However, for now, it will continue to be an essential part of clinical decision-making, especially due to the particularities of the authorization conditions and reimbursement for medicines in different countries.

The abovementioned patients can be considered as patients for whom platinum might not be the best option[8]. The available non-platinum-based therapies include single agents such as PLD, paclitaxel, and gemcitabine, and just one combination, trabectedin + PLD (Fig. 2).

It is expected that in more advanced lines there will be a greater proportion of patients for whom platinum may not be the best option, since patients must face a decrease in platinum efficacy after each new treatment line and a cumulative increase in toxicity. Therefore, alternative treatments to platinum-associated therapies can be of special

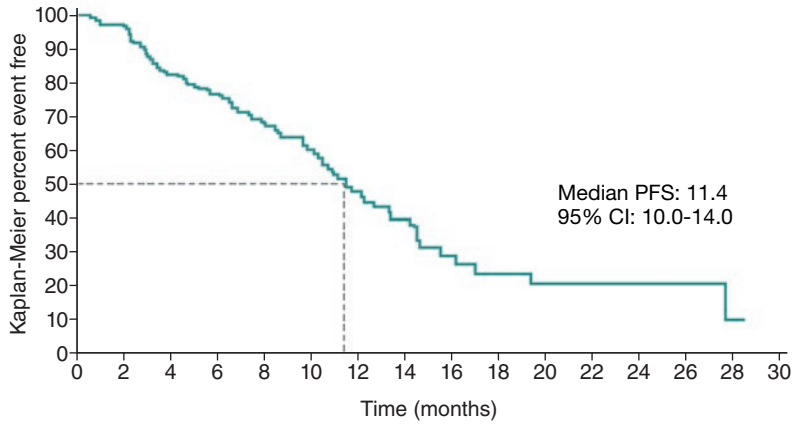

Figure 3. *PFS in the total population of the NIMES-ROC observational study* (modified from Pignata, et al.[9]).

help in advanced lines. An international, prospective, and observational phase 4 study is evaluating the use of trabectedin + PLD in women with recurrent ovarian cancer in clinical practice (NIMES-ROC)[9]. The recently presented preliminary results confirmed the data of previous clinical studies in a population more heavily pre-treated, in which 74.1% of patients were enrolled between the third and the seventh line of therapy. A median PFS of 11.4 months was reported (Fig. 3), similar to that of 9.2 months observed in the pivotal OVA-301 study (entirely performed in the second-line setting)[10].

Other efficacy parameters, such as ORR (38%) and disease control rate (66.5%), were also in line with the results of the OVA-301 study. Trabectedin + PLD was well tolerated, indeed the incidence of adverse events was slightly lower than that of the pivotal study. This is probably due to the greater experience in the use of trabectedin that has been accumulated over the years, especially in terms of both correct pre-medication with dexamethasone (from day –1 to day +4) and the management of dose adjustments, whenever necessary. Importantly, the enrolment data showed that 63.3% of treated patients had limited sensitivity to platinum[9]:

- Indicating that this is the population in which trabectedin + PLD is most frequently used in real-life practice
- Being aligned with the clinical data showing that these patients are the ones who benefit most from the combination

The ESGO-ESMO Consensus Conference on Ovarian Cancer considered the following criteria when defining the group of patients for whom platinum could be the best option[8]:

- Clinical response to the treatment (confirmed platinum sensitivity)
- Presence of a prior response to platinum without early symptomatic response (presumed/expected sensitivity)

For those patients highly symptomatic who have no contraindications for bevacizumab, the combination of platinum-based therapy with bevacizumab could be considered. Patients who have no priority for an urgent symptomatic response, or in whom bevacizumab is contraindicated, such as thrombosis and fistula should be offered a PARPi if they respond to platinum rechallenge, irrespective of their BRCA mutation status (Fig. 4)[8].

Response to previous therapy has to turn out to be a key factor when selecting a treatment, and it becomes even more relevant when aiming to use PARPi as maintenance therapy, as generally, only those patients who are in response to platinum are eligible for this treatment. Accordingly, it is necessary to assess the likelihood of a response to platinum rechallenge, particularly in patients who have shown a limited sensitivity to platinum[11]. In the CALYPSO trial, ORR in patients relapsing between 6 and 12 months after the previous platinum therapy was 45% with carboplatin + paclitaxel and 39% with carboplatin +

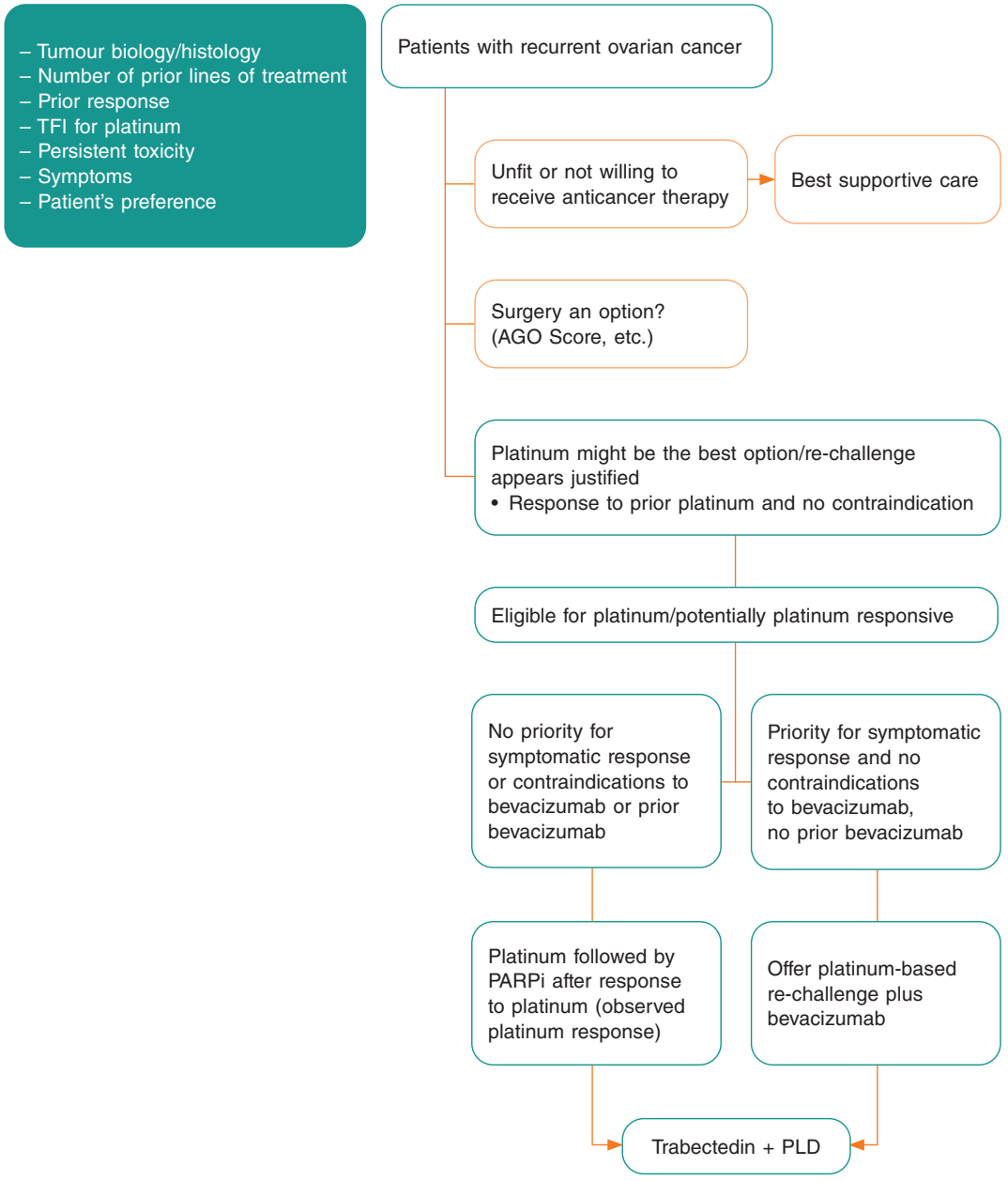

Figure 4. *Decision-making algorithm for the treatment of recurrent ovarian cancer when platinum might be the best option* (modified from Colombo, et al.[8]).

PLD[12]. Thus, it is difficult to be certain whether a patient with limited platinum sensitivity would meet the criteria for PARPi maintenance after platinum re-exposure[11].

The fact that only platinum responding patients were enrolled in the majority of PARPi pivotal studies is also important when putting data in context, as it prevents any comparison with other treatments tested in studies performed in patients who were in progression, with the worst prognosis. Indeed, results from a systematic review of randomized, controlled trials suggested that patients with ovarian

Table 1. *Efficacy outcomes according to response in patients with platinum-sensitive relapsed ovarian cancer treated with trabectedin + PLD or PLD monotherapy (data extracted from OVA-301 randomized phase III trial)*[14]

Treatment	Non-responders		Responders		p
Trabectedin/ PLD	N = 115		N = 103		
	Median PFS	5.4 months	Median PFS	12.7 months	<0.0001
	PFS at 12 months	8.4%	PFS at 12 months	52.4%	<0.0001
	Median OS	19.8 months	Median OS	Not reached	<0.0001
	OS at 36 months	15.4%	OS at 36 months	61.5%	<0.0001
PLD	N = 143		N = 69		
	Median PFS	3.7 months	Median PFS	10.1 months	<0.0001
	PFS at 12 months	9%	PFS at 12 months	33.8%	0.0002
	Median OS	19.4 months	Median OS	31.7 months	<0.0001
	OS at 36 months	25.4%	OS at 36 months	42.7%	0.0739

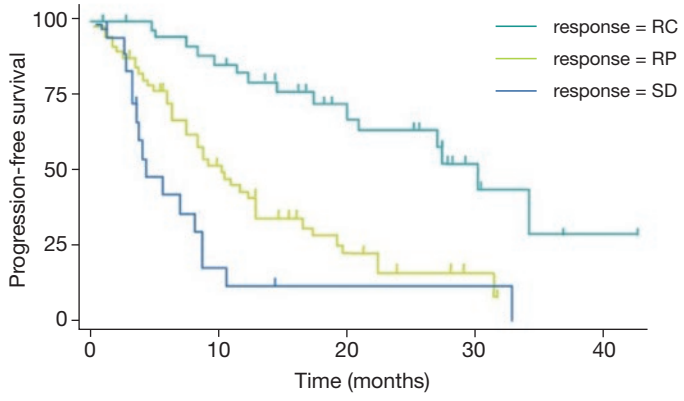

Figure 5. *PFS with olaparib as maintenance therapy according to response to platinum-based chemotherapy in BRCA-mutated patients with relapsed ovarian cancer* (modified from Intidhar S, et al.[15]).
SD: stable disease; RP: partial response; RC: complete response.

cancer who responded to chemotherapy (platinum or non-platinum based) tend to have the higher median OS and PFS compared with non-responders[13].

Thirty-nine studies were included in this analysis, representing 9,223 platinum-sensitive and resistant patients. Results showed that for every 10% increase in ORR, OS would increase by 2.83 months and PFS by 1.20 months.

The correlation between response to treatment and PFS and OS was also observed in the OVA-301 study[10] comparing trabectedin-PLD with PLD monotherapy (Table 1).

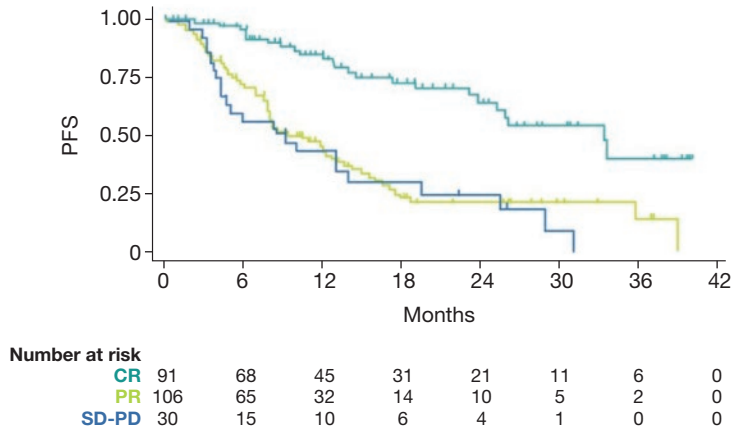

Figure 6. *Median PFS with olaparib as maintenance therapy in BRCA-mutated patients with relapsed ovarian cancer according to response to last platinum-based therapy* (modified from Cecere SC, et al.[16]).

Moreover, a similar correlation was observed between responses to platinum and the efficacy of PARPi. A multicenter retrospective study included 115 BRCA mutated ovarian cancer patients treated with olaparib as maintenance therapy after platinum-based chemotherapy[15]. Response to platinum was predictive for a prolonged PFS, achieving a PFS rate at 12 months of 79% in patients with a CR to platinum, 41% in patients with PR, and 12% in patients who only achieved stabilizations (Fig. 5).

Similar results have been obtained in a recent real-world study of olaparib as maintenance therapy after platinum that also included BRCA mutated patients with recurrent platinum-sensitive ovarian cancer (N = 234) (Fig. 6)[16].

As previously exposed, the newly generated maintenance data in the first-line setting will have an important impact on daily clinical practice. Since there are no available data of rechallenge with PARPi, it will also affect the management of recurrences. Another present challenge is to better understand the impact of PARPi in post-progression therapies. The above-mentioned real-world study of olaparib in 234 BRCA mutated patients[16] has shed some light on this matter. Patients progressing after olaparib and treated with chemotherapy had an unexpected poor RR:

- PFI > 12 months: ORR 22.2%
- PFI 6-12 months: ORR 11.1%
- PFI < 6 months: ORR 9.5%

These data of post-progression therapy seems to suggest cross-resistance with chemotherapy and need to be confirmed in larger studies[16].

The priority now is to evaluate current uncertainties to elaborate new treatment algorithms incorporating the novel options of PARPi and bevacizumab use in the first-line setting.

References

1. Romero I, Bast RC Jr. Minireview: human ovarian cancer: biology, current management, and paths to personalizing therapy. Endocrinology. 2012;153:1593-602.
2. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365:2473-83.
3. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379:2495-505.
4. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381:2391-402.
5. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Sevelda P, et al. Phase III PAOLA-1/ENGOT-ov25 trial: olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer (OC) treated with platinum-based chemotherapy (PCh) plus bev. Ann Oncol. 2019;30 Suppl 5:v851-934.
6. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as

maintenance therapy in ovarian cancer. N Engl J Med. 2019; 381:2403-15.
7. Hanker LC, Loibl S, Burchardi N, Pfisterer J, Meier W, Pujade-Lauraine E, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol. 2012;23:2605-12.
8. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol. 2019;30:672-705.
9. Pignata S, Scambia G, Mazzei T, Arruti Barbia M, Naglieri E, de Sande L. Trabectedin plus pegylated liposomal doxorubicin (PLD) in patients with platinum-sensitive recurrent ovarian cancer (PSROC): first results of an observational, prospective study (NIMES-ROC). Abstract n. 4449 ESMO 2018.
10. Monk BJ, Herzog TJ, Kaye SB, Krasner CN, Vermorken JB, Muggia FM, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol. 2010;28:3107-14.
11. Colombo N. Recurrent ovarian cancer 8 months after induction and bevacizumab consolidation: rationale for using trabectedin + pegylated liposomal doxorubicin in second line. Expert Rev Anticancer Ther. 2018;18:13-7.
12. Gladieff L, Ferrero A, De Rauglaudre G, Brown C, Vasey P, Reinthaller A, et al. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitive ovarian cancer patients: results from a subset analysis of the CALYPSO phase III trial. Ann Oncol. 2012;23:1185-9.
13. Siddiqui MK, Tyczynski J, Pahwa A, Fernandes AW. Objective response rate is a possible surrogate endpoint for survival in patients with advanced, recurrent ovarian cancer. Gynecol Oncol. 2017;146:44-51.
14. Data on file PharmaMar.
15. Intidhar S, de la Motte Rouge T, Derbel O, Kalbacher E, Wolfer A, Olivier T, et al. Predictive factors for prolonged response to olaparib as maintenance therapy in ovarian cancer patients with BRCA mutations Abstract n. 5558 ASCO 2018.
16. Cecere SC, Giannone G, Salutari V, Arenare L, Lorusso D, Ronzino G, et al. Olaparib as maintenance therapy in patients with BRCA 1-2 mutated recurrent platinum sensitive ovarian cancer: real world data and post progression outcome. Gynecol Oncol. 2020;156:38-44.

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