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Sensitivity and resistance to treatment in the primary management of epithelial ovarian cancer

Pierre-Emmanuel Colombo [a,*], Michel Fabbro [b], Charles Theillet [c], Frédéric Bibeau [d], Philippe Rouanet [a], Isabelle Ray-Coquard [e]

[a] *Department of Surgical Oncology, Montpellier Cancer Institute (ICM), 34298 Montpellier, France*
[b] *Departement of Medical Oncology, Montpellier Cancer Institute (ICM), 34298 Montpellier, France*
[c] *Identity and Tumoral Plasticity, (INSERM U896), Research Cancer Institute IRCM Montpellier Cancer Institute, 34298 Montpellier, France*
[d] *Department of pathology, Montpellier Cancer Institute (ICM), 34298 Montpellier, France*
[e] *Departement of Medical Oncology, Centre Léon Bérard, 69008 Lyon, France*

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Contents

Abstract

Ovarian carcinoma is the most lethal gynaecologic malignancy. Despite wide initial sensibility to chemotherapy especially to platinum-based regimens, the vast majority of patients with advanced stages of the disease develop recurrences and subsequent resistance to treatments.

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival; RFS, relapse-free survival; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; CCNE1, cyclin E1; ERCC1, excision repair cross-complementation group 1; HER2, human epidermal growth factor receptor-2; STIC, serous tubal intraepithelial carcinoma; MAPK, mitogen-activated protein kinases; K-RAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; B-RAF, v-raf murine sarcoma viral oncogene homolog B1; PTEN, phosphatase and tensin homolog; BRCA1/2, breast cancer gene 1 or 2; ARID1A, AT-rich interactive domain 1A gene; ASCO, American Society of Clinical Oncology; CTR1, copper transporter 1; GST, gluthatione S-transferase; NER, nucleotide excision repair; BER, base excision repair; PARP, poly ADP ribose polymerase; HR, homologous recombination; MRP2, multidrug resistance protein 2; GIST, gastro-intestinal stromal tumour; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3 related; FANCD2, Fanconi anaemia, complementation group D2.

* Corresponding author at: Department of Surgical Oncology, Montpellier Cancer Institute (ICM), 208 Rue des Apothicaires, Parc Euromedecine, 34298 Cedex 5, Montpellier, France. Tel.: +33 46 761 3114; fax: +33 46 761 8501.
E-mail addresses: Pierre-Emmanuel.Colombo@icm.unicancer.fr, pe.colombo@free.fr (P.-E. Colombo).

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Ovarian cancer is actually considered as a heterogeneous disease at the clinical, histological and molecular level. In this review, the mechanisms of intrinsic sensitivity or resistance to treatment, especially to platinum-based chemotherapy are considered with particular reference to the significance of tumour heterogeneity. The molecular features involved in acquired resistance are reviewed and the current hypotheses are discussed. In particular, potential disruptions of the DNA reparation pathways are highlighted.

Keywords: Ovarian cancer; Heterogeneity; Molecular subtypes; Resistance; DNA repair pathways

1. Introduction

Ovarian cancer (OC) is the main cause of gynaecological cancer death in developed countries. An insidious progression and the inability to perform effective screening [1] explain the late diagnosis at an advanced stage in 75% of cases, with tumour cell spread throughout the abdominal cavity in the form of peritoneal carcinomatosis (FIGO stages III–IV) [2]. Management of these tumours employs a combination of cytoreductive surgery and platinum-based chemotherapy [3]. Despite very high initial chemosensitivity and a frequent complete clinical response, the majority of patients with advanced OC relapse after a mean period of 18 months and progressively develop resistance to the various chemotherapeutic options [2,3]. The prognosis of these advanced stages thus remains grim, with the 5-year overall survival (OS) no more than 25–35% [2].

The systemic treatment of OC has changed little, if at all, since demonstration in the 1990s of the superiority of the cisplatin (or carboplatin) and paclitaxel combination, with a mean OS of around 38 months [4]. Studies have demonstrated that carboplatin could replace cisplatin with comparable efficacy, better tolerance and improved quality of life [5]. The carboplatin/paclitaxel combination has become the standard of care for first-line chemotherapy in EOC. Most attempts at improving this standard protocol, whether as consolidation chemotherapy by the addition of a third drug, or as maintenance chemotherapy after the six recommended cycles, have not demonstrated significant improvement with regard to survival and at the cost of poorer tolerance. To date, only the addition of bevacizumab (angiogenesis inhibitor targeting VEGF) to carboplatin/paclitaxel following a one-year maintenance phase was associated with improvement of relapse-free survival (RFS) in two randomised, prospective trials [6,7]. Nevertheless, this increase in efficacy remains modest, between 3 and 6 months, without significant impact on OS for all patients. It seems to mainly benefit patients with poor prognosis and macroscopic residual disease, as shown by an increase in OS in the ICON7 study [6]. The role of the antiangiogenic treatments (including bevacizumab and also other antiagiogenic treatments as nintedanib, pazopanib or trebananib) as maintenance therapy and results of on-going trials in EOC have recently been exhaustively reviewed in [8].

Many unresolved questions remain at this time regarding the management of advanced OC, and some of them are the source of recurrent clinical problems:

- At the initial stage, patient selection for an aggressive first surgery, or conversely, for neoadjuvant chemotherapy followed by interval debulking surgery, remains difficult. The only randomised clinical trial available to date found comparable OS and RFS between both of these strategies [9].
- Additional chemotherapeutic or targeted treatment individualised to tumour's biology are not available so far to improve the results of first-line systemic treatment.
- Finally, when relapse occurs, second- or third-line treatments are often determined empirically from the platinum drug-free interval between the end of the initial treatment and the recurrence [3,10].

Some of the different above-stated clinical problems could be resolved through better prediction of treatment response at the initial stage and at relapse. Such progress would then enable therapeutic management to be better individualised to the intrinsic characteristics of each tumour. In this review, we elaborate upon the main known factors and the current hypotheses in order to explain the clinical and biological heterogeneity of EOC and to understand the mechanisms that lead to the development of treatment resistance.

2. Inter-tumour heterogeneity of ovarian cancers

It has now been demonstrated that OCs are not a single clinical entity but are, from a clinical, histological and molecular standpoint, a heterogeneous group of tumours. At the initial stage, the prognosis for ovarian cancer is described in relation to three main related parameters [2,11]: (1) the patient herself, with age, general health state and the BRCA status if known playing a significant role; (2) the treatment results, with a major prognostic impact from the postoperative residual disease and the response to initial chemotherapy; (3) and finally the intrinsic characteristics of the tumour, in which many potential prognostic factors, both histological (histological subtype, FIGO stage, grade of differentiation, etc.) [12] and biological (hormone receptors, BRCA1/2 somatic mutations, VEGF, EGFR, CCNE1, ERCC1, HER2, molecular signatures, etc.) [13], have been described. Nevertheless, although tumour biology seems to be of prominent importance in this disease, there are no prognostic and/or predictive biomarkers that have been translated to date into clinical practice.