Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Updates and emerging therapies for rare epithelial ovarian cancers: One size no longer fits all ☆

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ARTICLE INFO

Article history:
Received 19 October 2014
Accepted 25 November 2014
Available online xxxx

Keywords:
Epithelial ovarian carcinoma
Low-grade serous carcinoma
Clear cell carcinoma
Mucinous carcinoma of the ovary
Endometrioid carcinoma
Chemoresistance

ABSTRACT

Epithelial ovarian carcinoma consists of not one, but several, entities. A number of subtypes exist, including high-grade and low-grade serous carcinomas, clear cell, endometrioid carcinoma and mucinous carcinoma. Historically, women with epithelial ovarian cancer have been treated similarly and "lumped" in the same cooperative group treatment trials, irrespective of their tumor subtype. Recently, however, differences in epidemiology, tumor biology, tumor marker expression and treatment responses have been elucidated among the histologic subtypes, with a clear distinction emerging between the Type I, lower grade tumors and Type 2, higher grade epithelial malignancies. A mounting body of research demonstrates that a "one-size-fits-all" treatment approach to epithelial ovarian tumors is no longer relevant, especially for the Type I subtypes. Indeed, with the exception of high-grade serous carcinoma, most other epithelial subtypes exhibit some degree of chemotherapy resistance, rendering treatment problematic, especially in the setting of advanced disease. This review summarizes the genetic, molecular, and clinical differences of the more rare, but clinically important, Type I epithelial ovarian tumors. Additionally, a critical appraisal of both historical and contemporary treatment approaches and the rationale for targeted therapies are emphasized.

Contents

☆ This is an invited manuscript. No industry, pharmaceutical or grant support was obtained to conduct this research or produce this manuscript. All authors contributed significantly to the manuscript design and execution.

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http://dx.doi.org/10.1016/j.ygyno.2014.11.078
0090-8258/© 2014 Published by Elsevier Inc.

Introduction

Ovarian cancer is diagnosed in approximately 22,000 individuals annually in the United States and is the 4th leading cause of cancer death among women [1,2]. Nearly 90% of ovarian malignancies are epithelial ovarian tumors of Mullerian origin [2]. Epithelial ovarian carcinoma consists of not one, but several, distinct entities [1,2], including high-grade serous carcinoma (70%), low-grade serous carcinoma (5%), clear cell carcinoma (11%), endometrioid carcinoma (11%) and mucinous carcinoma (3%) [3]. Historically, women with epithelial ovarian cancer have been treated similarly and "lumped" in the same cooperative group treatment trials, irrespective of their tumor subtype. Recently, however, differences in genetic profiles, tumor biology and treatment responses among the histologic subtypes have been discovered, with a distinction emerging between the Type I, lower grade tumors and Type 2, higher grade epithelial malignancies [4,5]. More contemporary studies demonstrate that a "one-size-fits-all" treatment approach to epithelial ovarian tumors may no longer be relevant, especially for the Type I subtypes. Indeed, with the exception of high-grade serous carcinoma, most other epithelial subtypes exhibit some degree of chemotherapy resistance, rendering treatment problematic, especially in the setting of advanced disease [4–15].

Recent developments in our understanding of the heterogeneity of epithelial ovarian malignancies, including refinement of pathologic criteria, elucidation of molecular and genetic tumoral differences, as well as disparate responses to treatment with chemotherapy, have led to the initiation of separate clinical trials for the epithelial histologic subtypes through the Gynecologic Oncology Group Rare Tumor Committee [2,3]. Despite this progress, substantive research on rare ovarian tumors remains logistically challenging, given the low overall patient numbers. This underscores the importance of coordinating efforts among cancer centers, and within the cooperative group setting, to define better treatment strategies for women with rare, but clinically important, ovarian malignancies. This review summarizes the differences among the rare epithelial subtypes and their management. Additionally, emerging therapies are highlighted, with an emphasis on low-grade serous carcinoma (LGSC), clear cell carcinoma (CCC), endometrioid carcinoma and mucinous carcinoma. The rationale for targeting the respective molecular pathways involved in these tumor subtypes is also discussed.

Origins and patterns of gene expression in the epithelial ovarian cancer subtypes

Scientists postulate that epithelial ovarian cancers originate from either a single cell layer covering the ovary, from the cells that line inclusion cysts beneath the ovarian surface or from the distal fallopian tube epithelium [16]. Cancers that develop from these cells may differentiate malignantly into four primary histologic subtypes: serous (both low- and high-grade), clear cell, endometrioid and mucinous. Morphologic similarity between these tumor types and differentiation of the normal epithelial cells in the gynecologic and intestinal tracts is noted by pathologists in several studies, including a resemblance between serous tumors and fallopian tube epithelium, endometrioid carcinoma to normal endometrial cells, clear cell cancers to vaginal rests and mucinous carcinoma to endocervical glands or intestinal mucosa [17].

Kurman and Shih suggest a dualistic model of carcinogenesis that divides epithelial ovarian carcinoma into two categories, Type I and Type II, based on molecular and clinicopathologic differences [18]. Type I tumors consist of low-grade serous carcinoma, endometrioid, clear cell and mucinous carcinomas, which develop in a stepwise fashion from well-described precursor lesions. Type I tumors possess activating mutations in *KRAS*, *BRAF*, *PI3KCA* and *PTEN*. Conversely, Type II tumors include high-grade serous carcinoma, carcinosarcoma and undifferentiated carcinomas, which are biologically more aggressive than the Type I tumors and often present with advanced stage disease. Type II tumors are characterized by genetic instability, mutations or epigenetic changes in *BRCA1* or *2* genes, with the high-grade serous tumors almost universally harboring mutations in *TP53*. These important genetic and molecular differences among the epithelial carcinoma subtypes lead to heterogeneic clinical presentations, patterns of spread and treatment responses. Therefore, accurate histologic subtype designation by experienced gynecologic pathologists is crucial to tailoring subtype-specific therapies.

Low-grade serous carcinoma

Epidemiology and histology

Serous carcinomas represent approximately 75% of all epithelial ovarian cancers, with approximately 70% characterized by high-grade disease [8]. Parity, breastfeeding, tubal ligation and oral contraceptive use have been associated with a decreased risk of the high-grade serous malignancies, but it is not clear whether these factors are related to low-grade serous carcinoma [19–21]. Studies demonstrate that histologic grade is one of the most important prognostic factors in epithelial ovarian cancer. Historically, the serous epithelial ovarian cancers were graded utilizing a three-tiered grading system (i.e. grades 1, 2 and 3) [6]. However, recently, a two-tiered system (low- vs high-grade) was proposed independently by Malpica as well as Kurman and Shih and is now commonly used [7]. This system is based primarily on assessment of nuclear atypia and mitotic rate (Table 1), with the

Please cite this article as: Groen RS, et al, Updates and emerging therapies for rare epithelial ovarian cancers: One size no longer fits all, Gynecol Oncol (2014), http://dx.doi.org/10.1016/j.ygyno.2014.11.078