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Review

Circulating and disseminated tumor cells in ovarian cancer: A systematic review

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HIGHLIGHTS

- CTCs and DTCs can be enumerated and identified in patients with ovarian cancer.
- Their presence in patients with ovarian cancer tends to be associated with adverse clinicopathological factors.
- Prospective validation is necessary for CTCs and DTCs to qualify as useful clinical biomarkers.

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ABSTRACT

Objectives. Detecting circulating tumor cells (CTCs) in the peripheral blood and disseminated tumor cells (DTCs) in the bone marrow of cancer patients has proven feasible and of prognostic value in different neoplasms. However, the clinical significance of CTCs and DTCs in ovarian cancer and its association with outcome remains unclear.

Methods. A literature search in PubMed was performed from January 2000 to December 2013 for studies evaluating CTCs and/or DTCs and its association with clinicopathological characteristics and clinical outcome in ovarian cancer. The main outcome measures were progression-free survival (PFS) and overall survival (OS).

Results. Fourteen studies met the inclusion criteria. Median study size was 84 patients (range 43–216). Median follow-up was 19 months (range 5–52). Most studies were small case series ($n < 100$; studies; 71%). The majority of studies used an immunophenotyping approach to identify CTCs and/or DTCs, but only 3 studies (21%) used the FDA-approved Cell Search method. Despite the differences in methodology among studies the presence of CTCs and DTCs tended to be associated with higher baseline CA-125 serum levels, higher odds of residual disease after surgery, and worse survival in ovarian cancer across studies. No consistent intra-patient correlation was observed between DTCs detected in the bone marrow and CTCs detected in the blood.

Conclusions. The presence of CTCs and DTCs is associated with adverse clinicopathological characteristics and poor clinical outcomes in ovarian cancer patients. Its implementation as a valuable prognostic tool in the clinical setting requires uniform methodology and prospective validation.

Contents

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Introduction

The majority of women with advanced ovarian cancer experience disease relapse despite aggressive cytoreductive surgery and chemotherapy. To date, only bevacizumab (and more recently, pazopanib) has proven to be an effective maintenance treatment after first-line chemotherapy in ovarian cancer, although no predictive factors of efficacy or toxicity have yet been described [1–3]. In retrospective analyses the CA-125 nadir (and its variations, even within normal limits) after primary treatment seems to represent a valuable prognosticator of disease recurrence [4–6]. The identification of novel and more informative prognostic factors in ovarian cancer should ideally translate in better patient stratification according to their risk of relapse and eventually, in more individualized treatments.

The detection and quantification of circulating tumor cells (CTCs) has raised considerable interest over the last decade as a potential prognostic and predictive biomarker in solid tumors. CTCs are isolated tumor cells disseminated from the site of disease in metastatic and/or primary neoplasms that can be identified in the peripheral blood. Previously to the identification of CTCs, the presence of isolated epithelial ovarian cancer cells in the bone marrow has been studied using immunocytochemical techniques. These cells, named disseminated tumor cells (DTCs), were considered to be the potential precursors of subsequent metastatic disease [7]. It is unclear whether CTCs and DTCs represent identical cell populations but observed at a different anatomic location (i.e. bone marrow and bloodstream, respectively) and a distinct stage of tumor progression. While DTCs might involve an active process of cancer cell implantation in a metastatic niche, CTCs may represent both passive shedding and active shedding of tumor cells from the tumor. CTCs and DTCs may have indeed different phenotypic characteristics and also distinct clinical significance in clinical outcome.

Initial studies focused primarily on characterizing DTCs and their clinical significance in the course of the disease [8]. Such interest shifted towards the detection and identification of CTCs mainly due to the relative ease of collection, quantification and monitoring with non-invasive methods. Landmark studies in metastatic breast cancer showed that elevated CTC counts are consistently associated with shortened survival [9–11]. Further prospective studies and meta-analysis have confirmed the prognostic value of CTCs also in colorectal and prostate cancer [12–14]. However, despite the robust association observed between the presence of CTCs and clinical outcome in many cancers, the clinical application of CTCs in the daily practice has not yet been fully incorporated [15].

The present systematic review aims to summarize the key findings of all published clinical studies evaluating CTCs and DTCs in ovarian cancer and its association with clinicopathological characteristics and outcome. The potential future applications of CTCs and DTCs in the clinical management of ovarian cancer will also be discussed.

Methods

Search strategy

A literature search in Medline (host: OVID) from January 2000 to December 2013 for articles evaluating CTCs and ovarian cancer was performed using keywords and MeSH terms. MeSH terms included "Ovarian Neoplasms" and "Neoplastic cells, circulating". Keywords included "ovarian cancer"; "ovarian carcinoma"; "circulating tumor cells"; and "disseminated tumor cells". Searches were limited to human studies and English language publications. Citation lists of retrieved articles were checked to ensure sensitivity of the search strategy.

Study selection

Eligibility criteria included articles published in peer-reviewed journals that assessed the relationship between CTCs in ovarian cancer and clinicopathological characteristics and/or reported outcomes of interest (overall survival [OS], progression-free survival [PFS], disease-free survival [DFS]). Commentaries, single case-reports, editorials, review articles, small sample size studies ($n < 30$), unrelated articles and duplicates were excluded (Fig. 1). One reviewer (N.R.) evaluated all the titles and abstracts identified by the search strategy, and all potentially relevant publications were retrieved in full. Two reviewers (N.R. and I.D-P.) then independently assessed the articles for study eligibility. After preliminary review of articles for study inclusion, inter-reviewer agreement was assessed with the Cohen's kappa (κ) coefficient [16]. Disagreement was resolved by consensus.

Data extraction

For eligible studies pre-specified data elements included the following: author, year of publication, journal citation, country, inclusion and exclusion criteria, study design and methodology; distribution of clinicopathological factors (including patients' age, tumor histology, tumor grade, International Federation of Gynecology and Obstetrics [FIGO] stage, and residual disease after cytoreductive surgery), details regarding therapeutic interventions (type of surgery, chemotherapy agents); duration and completeness of follow-up; methodology for CTC and/or DTC isolation and characterization (including but not limited to timing of cell extraction, cell surface markers, antibodies used for detection of positive cells, and definition of positive thresholds); analytical strategy (including whether multivariate analysis was performed) and association between CTCs and/or DTCs and outcome(s) of interest. Relationships with surrogate and unconventional outcomes were excluded.

Assessment of bias of included studies

The risk of bias of the studies included in this review article was assessed according to the following criteria: (i) study design; (ii) whether or not patients included in analyses were representative of the larger population of ovarian cancer patients in a similar clinical setting (external validity); and (iii) whether or not bias within the study design and analysis was appropriately considered (i.e. internal validity).

Results

Characteristics of included studies

Fourteen studies were included in the final analysis (Table 1). When selecting the studies to be included in this review, there was a high grade of concordance between reviewers ($\kappa = 0.9$). In general, studies included a representative sample of the global patient population in