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Clinical Commentary

Moving beyond the platinum sensitive/resistant paradigm for patients with recurrent ovarian cancer

HIGHLIGHTS

- It is timely to reconsider how patients with recurrent ovarian cancer are classified.
- Categorizing recurrent ovarian cancer patients only on basis of a timeline is limited.
- A multiplex system of categorizing patients with recurrent ovarian cancer is needed.

Keywords:
Recurrent ovarian cancer
Platinum sensitive/resistant

1. Introduction

In 1991, Markman et al. published a landmark article that evaluated the response of patients with recurrent ovarian cancer to a second cisplatin-based regimen [1]. In this study, patients with a longer platinum free interval had higher response rates to retreatment with platinum-based chemotherapy [1] (Table 1). This study, along with others [2,3], essentially codified the classification system of platinum sensitive versus platinum resistant used over the ensuing decades to categorize and plan treatment for patients with recurrent ovarian cancer. Recurrent ovarian cancer patients with a platinum free interval (measured from last infusion of a platinum in primary treatment to documentation of recurrence) of six months or greater were categorized as "platinum-sensitive" while those patients with a platinum free interval of less than six months were categorized as "platinum-resistant." The implication was that retreatment with platinum in patients with "resistant" disease was unlikely to have significant benefit, whereas objective response rates were higher and more achievable with platinum retreatment in patients categorized as "sensitive". This classification schema has served for over the past two decades as a practical guideline for managing patients predominantly in the setting of second or third line treatment when treatment options were more limited. In addition, this classification schema became embedded in the design of and eligibility criteria for hundreds of clinical trials and since the early 1990's has served as the basis of drug approvals by regulatory agencies for patients with recurrent ovarian cancer. These events served to further solidify how patients with recurrent ovarian cancer have been categorized and managed.

However, perhaps it is the ideal time to rethink how patients with recurrent ovarian cancer are classified. The rationale for classifying patients with recurrent ovarian cancer should focus on two key considerations. First, the designation of a patient with recurrent ovarian cancer as either platinum sensitive or platinum resistant based solely on a time line is severely limited. Second, the remarkable discoveries in molecular genetics over the past decade plus have significantly enhanced our understanding of how the biology of ovarian cancer modulates response to therapy in the recurrent setting. These considerations serve as the basis to challenge the traditional classification paradigm in recurrent ovarian cancer.

2. Rationale #1 — the designation of a patient with recurrent ovarian cancer as either platinum-sensitive or platinum-resistant solely on the basis of a time line is severely limited

The time of diagnosis of recurrence in a patient with ovarian cancer can be quite variable and highly dependent upon how cancer surveillance in performed. Indeed, surveillance guidelines published by the Society of Gynecologic Oncology (SGO) and the National Comprehensive Cancer Network (NCCN) provide no standard means of monitoring ovarian cancer patients for recurrence (Table 2) [4,5]. These guidelines recommend that ovarian cancer patients undergo review of symptoms and physical examination at regular time intervals that generally vary between 2 and 6 months for five years following completion of primary therapy. Following patients with intermittent CA125 serum testing is deemed optional by the SGO and acknowledged by the NCCN to be controversial primarily based upon the study of Rustin et al. who demonstrated no long-term survival advantage of using intermittent CA125 serum testing to monitor ovarian cancer patients for recurrence [6]. Despite the results of this singular and unique study, clinicians still utilize CA-125 to monitor patients for recurrence of ovarian cancer in most parts of the world.

The SGO guidelines also state that there is insufficient data to recommend routine use of radiographic imaging studies to monitor an asymptomatic ovarian cancer patient who has completed her initial surgery and platinum-based chemotherapy and has no clinical evidence of recurrence. The NCCN recommends imaging studies be performed only when clinically indicated. Imaging technology has become increasingly more sophisticated and is vastly more sensitive for the detection of recurrence in patients with ovarian cancer than that available when Markman et al. was published [1]. The resolution of computed tomography (CT) has increased significantly over the past two decades with the incorporation of higher slice systems, new detector technology, and

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Table 1
Summary of responses in ovarian cancer patients receiving a second cisplatin-based regimen.[a]

Cisplatin-free interval	Assessable (n)	Total response (n/%)	Surgical complete response (n/%)
5–12 months	22	6 (27%)	1 (5%)
13–24 months	18	6 (33%)	2 (11%)
>24 months	32	19 (59%)	7 (22%)

[a] Adapted from Markman et al. [1].

spectral CT imaging. The advent of Positron Emission Tomography (PET) and PET/CT imaging has also improved the ability of clinicians to more reliably detect recurrence of ovarian cancer and the extent of disease [7]. These improvements in imaging technology have made the once common clinical scenario of "biochemical" recurrence of ovarian cancer defined as an elevated CA125 above the normal level with normal imaging studies less common. Indeed, there is increasing evidence that recurrence of ovarian cancer can be detected in patients with rising CA125 values within the normal range utilizing improved imaging technology [8,9]. Furthermore, while there are cases where imaging confirms recurrence before or even without a CA 125 rise, there are numerous instances where CA 125 can confirm recurrence prior to imaging with median lead times previously reported to be approximately 3 months [10]. This relationship is depicted conceptually in Fig. 1. Additionally imaging can result in false positive results due to the patterns of recurrence in ovarian cancer with often very small volume disease or no disease potentially leading to unnecessary surgery and/or systemic treatment.

Thus, the time to the diagnosis of recurrence of ovarian cancer is highly dependent upon how a patient is monitored after primary treatment by their oncologist and can significantly impact how a patient with recurrent disease is classified and clinically managed. As demonstrated in Fig. 2, a patient could theoretically be designated as platinum sensitive if CA125 or imaging studies are obtained only with clinical evidence of recurrence. The same patient might be considered as less platinum-sensitive if recurrent disease detected with imaging obtained with a rise above normal of routinely obtained CA125 levels or as even platinum-resistant, if recurrent disease detected with imaging obtained with a rise within the normal range of routinely obtained CA125 levels. In addition, it is clear that response to platinum re-induction is neither categorical nor binary; rather expectation of therapeutic response represents a continuum. Indeed, the ICON 4 trial demonstrated that approximately 60% of patients deemed platinum sensitive responded to repeat use of platinum [11] and there is evidence of response to repeat platinum use in the setting of platinum resistant cancer [12,13]. The key concept is that neither CA 125 nor imaging is completely reliable for detecting recurrence for all patients, and the variable application of these two modalities both in clinical practice and in clinical trial design and conduct severely limits the accuracy of the traditional time-line based classification system. One could minimally skew the recurrence time with these tools, and thereby completely alter the designation of platinum sensitive versus resistant.

Table 2
SGO and NCCN guidelines for posttreatment surveillance of ovarian cancer patients.[a]

Monitoring intervention	SGO	NCCN
Review of symptoms and physical examination	Every 3 months yrs 1–2 Every 4–6 months yr 3 Every 6 months yrs 3–5 Annually yrs >5	Every 2–4 months yrs 1–2 Every 3–6 months yrs 3–5 Annually yrs >5
CA125	Optional	If initially elevated (with caveat regarding utility)
Imaging studies	Insufficient data to support routine use	As clinically indicated

[a] Adapted from Salani et al., [4] and Morgan et al., [5].

Of note, ovarian cancer patients are often currently managed with multiple sequential therapeutic regimens. The manner by which these patients are surveyed after their first or second recurrence could have an even greater impact on subsequent management decisions. The designation of platinum-sensitive vs. platinum-resistant on the basis of a time line in the patient with recurrent ovarian cancer beyond the third line of therapy may be less precise or important. For example, olaparib was recently approved for patients with a *BRCA* mutation who have been treated with three prior chemotherapy regimens regardless of the prior treatment free interval or platinum sensitivity or resistant status.

3. Rationale #2 — there is an enhanced understanding of how the biology of ovarian cancer affects response to therapy in the recurrent setting

Over the past decade, there has been increasing evidence that there are factors beyond just the treatment free interval that impact how patients with recurrent ovarian cancer respond to further therapy. Histologic subtype of ovarian cancer is clearly one of those factors. Mucinous, clear cell, and low-grade serous carcinomas are all known to be less responsive to chemotherapy in both the primary and recurrent settings and reflect distinct entities with differing natural histories [14].

BRCA1/2 mutation status is also a factor that is known to affect outcomes in patients with ovarian cancer [15]. In the recurrent setting several lines of evidence suggest that ovarian cancer patients with a somatic or germline *BRCA1/2* mutation are highly responsive to platinum and other DNA-damaging chemotherapy regimens. The earliest indication of this phenomena was a 1997 publication by Markman et al. who reported a series of ovarian cancer patients who remained sensitive to repeated treatment with platinum [16]. This preceded routine *BRCA* mutation testing in ovarian cancer patients. Alsop et al. subsequently demonstrated that 8 of 10 ovarian cancer patients with germline *BRCA1/2* mutations responded to platinum-based chemotherapy even though technically defined as platinum-resistant on the basis of traditional treatment free interval criteria [17].

Recurrent ovarian cancer patients with *BRCA1/2* mutations are also generally more responsive to other chemotherapy agents that induce direct DNA damage and specifically to targeted agents such as PARP inhibitors. Safra et al. demonstrated an enhanced time to treatment failure and improved overall survival to second and third line treatments with pegylated doxorubicin in a series of 40 recurrent ovarian cancer patients with a *BRCA1/2* mutation [18]. Kaye et al. also demonstrated a higher than expected PFS in recurrent ovarian cancer patients with a *BRCA1* or *BRCA2* mutation treated with pegylated doxorubicin [19]. Kaufman et al. demonstrated an overall response rate of 73% to the PARP inhibitor olaparib in 193 recurrent ovarian cancer patients with a known deleterious germline *BRCA1/2* mutation [20]. What made this response rate so

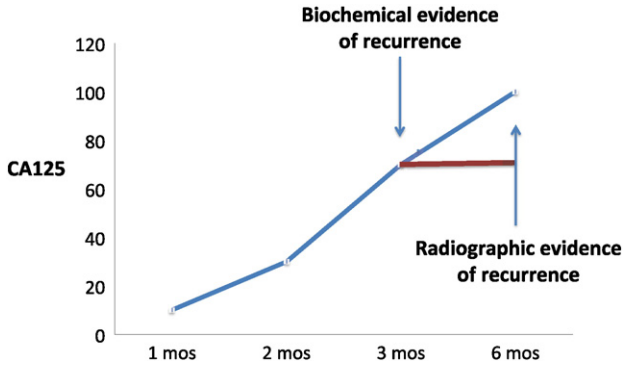

Fig. 1. Conceptual depiction of lead-time between rising CA125 and clinical detection of recurrent disease with imaging in a typical patient with a CA125 over-expressing ovarian cancer.