Audit of CA125 Follow-Up After First-Line Therapy for Ovarian Cancer

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Aims: The Medical Research Council OVO5/EORTC 55955 trial showed that patients in remission after first-line therapy for ovarian cancer did not benefit from routine measurement of CA125 during follow-up. Since the presentation of these results, we have counseled patients about the options for follow-up and provided them with an information leaflet about the trial results and the symptoms that should prompt an early appointment and CA125 measurement. We present an audit of practice after the presentation of those results.

Methods: The medical records of 143 consecutive patients completing first-line therapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer in our unit between July 2009 and December 2013 were analyzed.

Results: An agreed plan of CA125 follow-up was recorded in 69 (79%) of 87 eligible patients on completion of first-line therapy. No routine CA125 follow-up was selected by 55 (80%) patients, and routine CA125 follow-up was selected by 14 (20%), of whom 3 wished not to be informed of the results. CA125 levels were checked in 28 (51%) patients in the no routine CA125 follow-up group, in 26 cases because of the development of symptoms. Relapse was confirmed in 22. Median follow-up was 360 days (range, 100–836). CA125 levels were checked in all 14 patients who had requested routine CA125 follow-up. Relapse has been confirmed in 2 patients. Median follow-up was 560 days (range, 500–620).

Conclusions: If patients are given sufficient information about the role of routine CA125 measurements during follow-up, the majority decide against CA125 monitoring and hence, avoid these blood tests.

Key Words: Ovarian cancer, CA125, Monitoring, Screening, Counseling, Tumor markers

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CA125 is performed every 3 months for 2 years, then every 6 months up to 5 years.

CA125 is a valuable marker in the initial diagnosis and monitoring of response to chemotherapy in epithelial ovarian cancer, and regular CA125 measurement after completion of primary therapy can detect cancer recurrence several months before a patient experiences symptoms or exhibits signs of disease.3–6 Indeed, the Gynecologic Cancer InterGroup defines recurrence on the basis of a doubling in serum CA125 levels to more than twice the upper limit of normal or to more than twice the nadir if never within the normal range,3 with an elevated value being confirmed by 2 separate measurements obtained at least 1 week apart. However, although the benefit of CA125 monitoring during therapy and its role in diagnosing relapsing disease is not disputed, there are questions as to the value of routine CA125 monitoring after completion of treatment.

The value of routine CA125 monitoring was examined in the OVO5/EORTC 55955 study of women who had achieved complete remission after first-line platinum-based chemotherapy. This large randomized trial compared the earlier intervention of second-line treatment based on increased CA125 levels with delaying treatment until clinical evidence of relapse. The study demonstrated no overall survival benefit of early CA125-driven treatment.7 Indeed, women assigned to delayed treatment started chemotherapy 4.8 months later than those assigned to early treatment, with no detriment to overall survival, whereas early treatment was detrimental to quality of life.7 The counterintuitive results of the OVO5/EORTC 55955 study led to a variety of criticisms about the trial and its conclusions, which have been vigorously defended.8

Since the presentation of the OVO5/EORTC 55955 results, we have counseled patients at our institution about their follow-up at completion of their first-line chemotherapy. We have offered them 3 options for follow-up: (1) not to have routine CA125 measurements providing they are well and have no symptoms suggesting relapse, (2) to continue having routine CA125 measurements but not to be told the result unless requested by the patient (particularly suitable for patients on clinical trials, where regular CA125 measurements are mandated), and (3) to have routine CA125 measurements and be told the results. We provided them with an information leaflet outlining the rationale for follow-up, why we recommend not having routine CA125 measurements, and the symptoms that should prompt an early appointment and CA125 measurement (appendix 1, http://links.lww.com/IGC/A456). We present an audit of practice at our institution since the presentation of the OVO5/EORTC 55955 results.

METHODS

Patients who had completed first-line therapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer in our unit between July 2009 and December 2013 were identified from a preexisting database. The medical records of 143 patients who met these criteria were then analyzed (Fig. 1). Six (4%) of these patients did not receive first-line chemotherapy, 23 (16%) did not achieve remission (residual disease on computed tomography [CT] or persistently elevated CA125), and 27 (19%) were not followed up in our unit after completion of first-line therapy. These patients were excluded from further analysis.

The study demonstrated no overall survival benefit of early CA125-driven treatment based on increased CA125 levels with delaying treatment until clinical evidence of relapse. The number of CT scans performed during follow-up in each group was also recorded as was the indication for the scan and the scan result (recurrence vs no recurrence). The number of patients who relapsed in each group was established, and the first indicator of relapse was recorded, namely: rising CA125 levels; development of new signs; or development of new symptoms.

Finally, the start date of second-line chemotherapy or salvage surgery was documented, and the patient’s status (alive or deceased) at the time of data collection was recorded.

RESULTS

A total of 87 (61%) of the 143 patients analyzed were eligible for inclusion in the study. Evidence of a discussion about the pros and cons of CA125 monitoring and an agreed CA125 follow-up plan were recorded in 69 (80%) of the 87 eligible patients on completion of first-line therapy. Of these 69 patients, no routine CA125 follow-up was selected by 55 (80%), and routine CA125 follow-up was selected by 14 (20%). Eleven (79%) patients who opted for routine CA125 follow-up requested that they be informed of the results, and 3 (21%) wished not to be informed.

The “No Routine CA125” Monitoring Group

The average age of patients in the “no routine CA125” monitoring group at completion of first-line chemotherapy was 65.3 years (range, 48–85) (Table 1). The average end-of-treatment CA125 level was 16.9 (range, 7–35). Forty-three (78%) patients lived with another family member, and 12 (22%) patients lived alone. Fifteen (27%) were employed at diagnosis, 12 (22%) were retired, 23 (42%) were not employed, and in 5 (9%) cases, the employment history was not documented.

In total, CA125 levels were checked in 28 (51%) patients in the no routine CA125 monitoring group during follow-up after completion of first-line therapy. In 26 (93%) cases, CA125 testing was instigated because of the development of symptoms, in 1 (3.5%) case because of the development of clinical signs, and in 1 (3.5%) case, specifically
at the patient’s request. Relapse was detected in 21 (75%) of those who had a CA125 test performed. Relapse was also detected by CT scan in 1 patient without a CA125 level being checked in advance.

Hence, overall, 22 (40%) patients in the no routine CA125 follow-up group relapsed after completion of first-line therapy. The first indicator of relapse was symptoms in 21 (95%) and signs in 1 (5%). The average CA125 level at relapse was 346 (range, 41–1656).

Twenty (90%) of the patients who relapsed subsequently underwent second-line chemotherapy, and 1 (5%) patient underwent salvage surgery. The mean treatment-free interval was 395 days. At the time of data collection, 12 (55%) of 22 relapsed patients remained alive and under follow-up, 9 (40%) of 22 had died, and 1 (5%) of 22 was lost to follow-up at completion of second-line therapy.

The “Routine CA125” Monitoring Group
The average age of patients in the “routine CA125” monitoring group at completion of first-line chemotherapy was 56 years (range, 46–68). The average end-of-treatment CA125 level was 13 (range, 7–24). Twelve (86%) patients lived with another family member, and 2 (14%) patients lived alone. Eight (58%) patients were employed at diagnosis, 3 (21%) were retired, and 3 (21%) were not employed.

CA125 levels were checked in all 14 (100%) patients who had requested routine CA125 follow-up. The indication for CA125 measurement was planned follow-up in all cases, although 1 patient had also developed symptoms at the time of routine CA125 monitoring. Relapse was detected in 2 (14%) of those who requested routine CA125 measurements. Both relapsed patients underwent second-line chemotherapy. The mean treatment-free interval was 585 days, and the average CA125 level at relapse was 39 (range, 35–43).

At the time of data collection, both patients remain alive and under follow-up.

| No Routine CA125 Follow-Up | Routine CA125 Follow-Up |
|----------------------------|-------------------------|
| No. patients               | 55                      | 14                       |
| Average age (range), y     | 65 (48–85)              | 56 (46–68)               |
| Tests prompted by symptoms | 26/28 having CA125 measured | 0/14 having CA125 measured |
| Number relapsing           | 22                      | 2                        |
| Number with raised CA125 at relapse | 21 | 2 |
CONCLUSIONS

This audit shows that if patients who have completed first-line chemotherapy for ovarian cancer are appropriately educated and counseled about follow-up, the majority opt not to have routine CA125 measurements. Since the results of the MRC OVO5/EORTC 55955 trial were presented, it has been our recommendation to patients not to have routine CA125 measurements. At the same consultation that we discuss follow-up options, we also give patients a leaflet that provides information on why we carry out follow-up, the different follow-up options, and a list of symptoms that should prompt an earlier appointment (Appendix 1, http://links.lww.com/IGC/A456). Aspects that are frequently discussed include the management dilemma of a woman with a rising serum CA125 concentration who remains well and asymptomatic. The results of the MRC OVO5/EORTC55955 trial suggest that as long as the patient is well and there is no evidence of current or impending compromised organ function, it is reasonable to delay chemotherapy. Although patients are reassured by the finding of a normal CA125 reading, many find routine CA125 measurement to be a major source of anxiety. The guidelines produced by various oncological organizations at least now suggest that patients should be offered a choice, although some are more in favor of routine CA125 measurements than others.

It seemed that those who accepted our advice were older and had a higher relapse rate than those who opted for routine CA125 measurements. No association could be demonstrated between tumor stage, grade and histological subtype, and choice of CA125 monitoring in this audit. However, the study may have been underpowered to detect such an association. We had insufficient numbers to determine whether factors such as future planning for work, family events, or holidays influenced patients’ decisions related to follow-up options.

Since the OVO5/55955 trial was completed, bevacizumab, given with first-line carboplatin and paclitaxel and then as maintenance therapy, has been shown to improve survival in a high-risk subgroup of patients with ovarian cancer. It is standard practice to monitor for tumor progression with 3 or 6 weekly CA125 measurements while on bevacizumab maintenance therapy, even though a rising level should not on its own lead to discontinuation of bevacizumab. Once patients complete bevacizumab maintenance with maintained remission, they can continue follow-up without the need for routine CA125 measurements. Majority of women are currently not receiving maintenance therapy so do not require routine CA125 monitoring.

If there was a system that could improve survival outcomes and provide a choice to patients with relapsed ovarian cancer and the improvement in survival was dependent on the tumor volume being as small as possible, it would then be advisable to perform routine CA125 monitoring. Unfortunately, although several therapies have been shown to improve progression-free survival, no therapy for relapsed ovarian cancer has so far been shown to significantly improve survival. Retrospective data from the AGO-DESKTOP trial demonstrated that cytoreductive surgery offered a survival benefit in patients if complete resection was achieved, highlighting the importance of being able to predict those patients in whom complete resection is a realistic goal. The first prospective surgical trial in recurrent ovarian cancer, AGO-DESKTOP II, validated a predictive score for complete resection, the “AGO score”, which may be a useful tool in selecting patients for secondary cytoreductive surgery. DESKTOP II showed that patients with an Eastern Cooperative Oncology Group PS0, no residual disease after surgery for primary ovarian cancer, and an absence of ascites preoperatively had a 76% likelihood of undergoing complete resection. The randomized prospective AGO-DESKTOP TOP III trial is currently underway investigating the role of surgery and chemotherapy versus chemotherapy alone in patients with recurrent platinum-sensitive ovarian cancer, the results of which may help to clarify whether cytoreductive surgery significantly improves survival in this patient group and identify which patients would benefit from this intervention. These results may in turn have an impact on the role of CA125 monitoring in follow-up.

We conclude that, when given sufficient information about the role of routine CA125 measurements during follow-up, the majority decide against CA125 monitoring and, hence, avoid these routine blood tests.

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