Prognostic role of platinum sensitivity in patients with brain metastases from ovarian cancer: results of a German multicenter study


1Department of Gynecology and Obstetrics, Charité-Campus Virchow Klinikum, University Medicine of Berlin, Berlin; 2Department of Gynecology & Gynecologic Oncology, Dr. Horst Schmidt Klinik (HSK), Wiesbaden; 3Department of Obstetrics and Gynecology, Justus-Liebig-University of Giessen, Giessen; 4Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg; 5Department of Obstetrics and Gynecology, Freiburg University Medical Center, Freiburg; 6Department of Gynecology and Obstetrics, Friedrich Schiller University, Jena; 7Department of Gynecology and Obstetrics, University Hospital Essen, Essen; 8Department of Radiation Oncology and Radiotherapy, Charité-Campus Virchow Klinikum, University Medicine of Berlin, Berlin, Germany

Received 3 February 2010; revised 14 March 2010; accepted 15 March 2010

Background: Ovarian cancer is the leading cause of death in women with gynecological malignancies. Brain metastases are considered an uncommon metastatic site. Only few data exist on prognostic factors for this patient collective.

Patients and methods: A multicenter retrospective chart review was carried out including all patients with histologically confirmed ovarian cancer from six different German hospitals from 1981 to 2008. Overall, 4277 cases of patients with ovarian cancer were screened and patients with brain metastases were identified and analyzed regarding various clinical variables and survival.

Results: A total of 74 women with brain metastases were identified, resulting in an incidence of 1.73%. In multivariate analysis, the following clinical parameters had a significant impact on overall survival: multiple lesions [hazard ratio (HR) 4.4, 95% confidence interval (CI) 2.0–9.7] and low grading (HR 3.1, 95% CI 1.7–5.8) were associated with a negative impact. Platinum sensitivity (HR 0.23, 95% CI 0.12–0.48) was significantly associated with a favorable outcome. Good performance status (60%–80% HR 0.48, 95% CI 0.23–0.99 and 90%–100% HR 0.21, 95% CI 0.08–0.53) also had a positive impact on overall survival.

Conclusions: Platinum sensitivity is the most important prognostic factor in patients with ovarian cancer metastatic to the brain. This novel finding should be considered in the strategy of multimodal therapy for brain metastases in ovarian cancer.

Key words: ovarian cancer, platinum sensitivity, prognostic factors

introduction

Ovarian cancer is one of the most challenging diseases in the field of gynecological oncology since it is the leading cause of mortality among genital cancer [1]. The disease is associated with a high rate of relapse and tumor-related death even after optimal cytoreduction and adjuvant therapy [2]. Recurrence usually presents in the abdomen with peritoneal or lymphatic spread and is rarely observed extraabdominally as a consequence of hematogeneous dissemination. Therefore, the central nervous system (CNS) is historically described as a very uncommon site of metastatic manifestation with an incidence of only 1%–2% of patients with epithelial ovarian cancer (EOC) [3–5]. As the overall survival from ovarian cancer is increasing due to advances in therapeutic management, patients are more likely to present with uncommon complications of the disease, such as brain metastases [6]. This implies a growing relevance of CNS relapse in patients with ovarian cancer and underlines the importance of a better understanding of this condition. Information regarding predictive and prognostic marker in this patient population is limited due to the rareness of brain metastases. Therefore, the present pooled multicenter analysis was initiated.

patients and methods

A multicenter retrospective chart review of patients with histologically confirmed EOC was carried out in seven German hospitals, including Charité-University Medicine Berlin, university hospitals of Freiburg, Jena, Giessen, Hamburg, Essen and the Dr. Horst Schmidt Klinik hospital in Wiesbaden in the period from 1981 to 2008. The medical charts were
Characteristic

- Age at time of diagnosis of brain metastases
  - 36 (48.6)
- Karnofsky index
  - <50%: 9 (12.2)
  - 50%: 11 (14.9)
  - 60%–80%: 38 (51.4)
  - 90%–100%: 16 (21.6)
- Serous histology: 53 (71.6)
- Grading I/II: 31 (41.9)
- Grading III: 43 (58.1)
- FIGO stage I/II: 12 (16.2)
- FIGO stage III/IV: 62 (83.8)
- Liver metastases: 21 (28.4)
- Ascites: 50 (67.6)
- No ascites: 24 (32.4)
- Single brain lesion: 26 (34.2)
- Multiple brain lesions: 48 (64.8)
- Platinum sensitive: 48 (64.9)
- Platinum resistant: 26 (35.1)
- Residual tumor after primary surgery
  - Microscopic: 43 (58.1)
  - Macroscopic: 31 (41.9)

Table 2. Symptoms from brain metastases in 74 patients with ovarian cancer

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>25 (33.7)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>16 (21.6)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>13 (17.5)</td>
</tr>
<tr>
<td>Seizure</td>
<td>12 (16.2)</td>
</tr>
<tr>
<td>Impaired vision</td>
<td>11 (14.8)</td>
</tr>
<tr>
<td>Paralysis</td>
<td>9 (12.1)</td>
</tr>
</tbody>
</table>

Table 3. Overview on multimodal therapy versus monotherapy

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OP</td>
<td>11</td>
<td>14.9</td>
</tr>
<tr>
<td>OP + CHEMO</td>
<td>2</td>
<td>2.7</td>
</tr>
<tr>
<td>OP + RT</td>
<td>14</td>
<td>18.9</td>
</tr>
<tr>
<td>OP + RT + CHEMO</td>
<td>21</td>
<td>28.4</td>
</tr>
<tr>
<td>RT</td>
<td>20</td>
<td>27.0</td>
</tr>
<tr>
<td>RT + CHEMO</td>
<td>6</td>
<td>8.1</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>100.0</td>
</tr>
</tbody>
</table>

OP, operation; RT, radiotherapy; CHEMO, chemotherapy.
Carboplatin was the chemotherapeutic agent in the fast majority of patients with chemotherapy.

The median follow-up period from date of initial diagnosis was 35.8 months (range 4–141 months), the median time of follow-up from date of diagnosis of brain metastases was 6.1 months (range 0.2–41.5 months). Sixty-eight of 74 patients (91.9%) died within the observation time. Median overall survival from primary diagnosis of EOC was 36.2 months (95% CI 33.3–39.1 months) and from diagnosis of brain metastases was 6.2 months (95% CI 4.9–7.5 months).

In multivariate analysis, five factors had significant impact on survival after diagnosis of brain metastases. Patients with multiple lesions had a fourfold risk of dying (HR 4.4, 95% CI 2.0–9.7) compared with patients with single lesions ($P < 0.001$) (Figure 1).

A high Karnofsky index at time of brain relapse was found to be related to a longer survival ($P = 0.004$). A Karnofsky index of 60%–80% and 90%–100% was related to a HR of 0.48 (95% CI 0.23–0.99) and 0.21 (95% CI 0.08–0.53), respectively, compared with a low performance status up to 50% (Figure 2). Patients with platinum-sensitive disease had a better survival (HR 0.23, 95% CI 0.12–0.46) than women with platinum-resistant disease even in the presence of brain metastases ($P < 0.001$) (Figure 3).

Additional factors that had significant impact on survival from diagnosis of brain lesions were tumor grading and FIGO stage. Patients with ‘low grade’ I and II had a shorter survival (HR 3.1, 95% CI 1.7–5.8) compared with patients with grade III ($P < 0.001$), and patients with advanced stages at first diagnosis of ovarian cancer had a better survival after diagnosis of brain metastases (HR 0.31, 95% CI 0.13–0.74) than those with stage I or II ($P = 0.011$). The following factors were not found to have any significant impact on survival from diagnosis of brain lesions: histology, age at primary diagnosis, ascites, residual tumor at primary surgery, extracranial disease at time of brain relapse and presentation with or without headache. The use of multimodal strategies did not translate into a significant prolongation of survival from diagnosis of CNS relapse (HR 0.57, 95% CI 0.31–1.05) when compared with women who had received monotherapy.

**Discussion**

The present study represents the largest cohort of patients with brain metastases from ovarian cancer reported to date. The incidence of brain metastases in our collective was 1.73%, correlating with the results of other series [4, 7, 8]. The assumption by some previous reports that the incidence of brain metastases from EOC is rising rapidly and approaching 12% cannot be supported by the findings of our study [9, 10]. However, the reported rates are most likely still underestimating the real incidence [11]. This may be due to the fact that brain imaging is not generally included in routine follow-up, and current analyses were derived from clinical observations.

**Figure 1.** Predicted survival since diagnosis of brain lesions for patients with single versus multiple brain metastases. Result of multivariate Cox regression; hazard ratio for patients with multiple lesions = 4.4 (95% confidence interval 2.0–9.7) compared with patient with single lesions ($P < 0.001$).

**Figure 2.** Predicted survival since diagnosis of brain lesions for patients dependent on the Karnofsky performance. Result of multivariate Cox regression; hazard ratio for patients with a Karnofsky index of 60%–80% and 90%–100% = 0.48 [95% confidence interval (CI) 0.23–0.99] and 0.21 (95% CI 0.08–0.53), respectively, compared with a low performance up to 50% ($P = 0.004$).

**Figure 3.** Predicted survival since diagnosis of brain lesions for patients with platinum-sensitive versus platinum-resistant disease. Result of multivariate Cox regression; hazard ratio for patients with platinum-sensitive disease = 0.23 (95% confidence interval 0.12–0.46) compared with patient with platinum-resistant disease ($P < 0.001$).
rather than autopsy studies. In the present study, we could observe a strong trend to more patients being diagnosed with brain metastases in the last third of the time period screened. This observation might be due to prolongation of overall survival in ovarian cancer and advances in imaging technology and availability of imaging technique [12, 13]. However, a bias due to an accumulation of patients with poorer outcome in the high-volume centers of the present study cannot be excluded.

In our retrospective analysis, data concerning response of treatment modalities were not evaluable due to the nature of the data accumulated over a period of 27 years. In the majority of patients, it was not possible to generate sufficient data such as imaging studies and other basic data sources to calculate reliable information on the response to the different treatment modalities and response evaluation was not systematically and consistently carried out.

A number of studies have been carried out in order to achieve a better understanding of patients with brain lesions from EOC to identify prognostic factors yielding inconclusive and controversial results [7, 8, 14]. A reproducible and accepted factor is the Karnofsky performance status [15]. It was demonstrated that a high performance status is likewise resulting in a higher median survival from the time of diagnosis of brain relapse [11, 15]. These findings are supported by the results of our study, which describes a significant correlation of a higher performance status with a longer median survival from diagnosis of brain metastases. Two other factors found to have a significant impact on survival in other studies could not be supported by the results of our analysis. One is the presence of extracranial disease at the time of brain relapse, which was found by Anupol et al. [7] and by Cohen et al. [4] to have a significantly negative impact. These findings could not be confirmed in our analysis, where we could not detect a significant difference between patients with or without extracranial disease with regard to survival from diagnosis of brain lesions: 6.2 months for patients with—versus 6.3 months for patients without—extracranial disease (P = 0.370). Another distinctive result of our study is the fact that no significant benefit in survival from diagnosis of brain relapse could be demonstrated for patients who had been treated with a multimodal approach in comparison to patients who had received a monotherapy. This finding is maybe related to the limited number of patients and is different to the reports of Cohen et al. [4] and Pectasides et al. [8] who found a benefit for patients who had been treated with a multimodal therapy modality in comparison to patients receiving monotherapy. It should be underlined that the comparison of these two collectives (monotherapy versus multimodal therapy) might be impaired by the inhomogeneity of the treatment applied to the different patients. Despite these facts, we did observe a trend for significantly longer survival in the multimodal treatment group. In most reports, a presentation with a single lesion promises a slight advantage, but this advantage does not reach statistical significance [7, 11]. In our study, patients with a single brain lesion had significantly favorable survival compared with patients with multiple lesions. In our analysis, we found a slightly improved survival since the diagnosis of brain metastases for patients with grade III tumors compared with grade I/II tumors. This finding was surprising since grade III tumors are usually linked to a poorer prognosis than low-grade tumors. Nevertheless, when we analyzed the interval of overall survival from primary diagnosis of ovarian cancer, there was no significant impact of grading on outcome. Furthermore, a potential selection bias in this cohort of patients with a very poor prognosis cannot be excluded. We also found an association between higher stage at primary diagnosis and slightly improved survival after diagnosis of brain lesions. This might be due to the fact that more patients with higher stage tumors at primary diagnosis die before they develop brain metastases. Those patients who live long enough to develop brain relapse might incorporate a selected group with positive basic characteristics that promise a selection bias compared with the group of early-stage tumors at primary diagnosis. However, this is only a hypothesis.

An interesting and novel finding of the current study is the fact that platinum sensitivity had a highly significant positive impact on survival from the diagnosis of brain metastases. The differentiation between patients who respond to platinum-based chemotherapy and patients who do not is well established in the clinical management of patients with recurrent ovarian cancer and the basis for the choice of systemic chemotherapy [16]. However, the role of platinum sensitivity has not been analyzed before in patients with brain metastases. One might propose that platinum resistance itself has such a detrimental impact on patient outcome that it overrules the effect of different treatment modalities in ovarian cancer patients with CNS metastasis. This observation that platinum sensitivity had a significant and relevant impact on survival in this very specific subgroup should be considered in the management of patients with brain lesions from EOC regarding multimodal treatment approaches.

conclusions

The most important finding of this study is the fact that platinum sensitivity had a highly significant positive impact on survival of patients with brain metastases from EOC. Based on the fact that this key factor in the management of EOC can be translated from the standard collective to this highly specific subgroup of patients with a very poor prognosis, future prospective studies should focus on a multimodal approach with special consideration of the previous response to platinum-based chemotherapy.

acknowledgements

This work has in part been presented at the American Society of Clinical Oncology meeting 2009.

disclosure

None of the authors declare conflicts of interest.

references


