Improving treatment strategies in ovarian cancer: Towards individualized patient care
van Meurs, H.S.

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Effectiveness of chemotherapy in measurable granulosa cell tumors: A retrospective study and review of literature

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M.R. Buist
A.M. Westermann
G.S. Sonke
G.G. Kenter
J. van der Velden
ABSTRACT

Objective

Patients with irresectable granulosa cell tumors (GCTs) often receive chemotherapy. The effectiveness of this approach, however, is uncertain. The aim of our study was to assess the response rate to chemotherapy for residual and recurrent inoperable GCT.

Methods

All consecutive chemotherapy-naive patients in 3 referral hospitals who were treated with chemotherapy for residual or recurrent GCT between 1968 and 2011 were included. Main outcome was the response according to Response Evaluation Criteria in Solid Tumor criteria. A literature search in MEDLINE through PubMed was performed, from inception to the August 19, 2013.

Results

Twenty-seven patients with a GCT who received chemotherapy were identified. Eighteen patients were not evaluable because they had either no measurable disease, or no imaging was performed before and after chemotherapy. One of the 9 evaluable patients (11%) had a complete response, and 1 patient (11%) had a partial response, resulting in a response rate of 22% (95% confidence interval, 0%-49%). Seven patients (78%) had stable disease (range, 2-50 months) and none had progressive disease. Fifteen studies that assessed response rates to chemotherapy on measurable disease in a total of 224 patients showed a response rate of 50% (95% confidence interval, 44%-57%). Strict criteria of response, however, were not uniformly applied in the majority of these published series.

Conclusions

In the present study, we present only a moderate beneficial effect of chemotherapy in patients with irresectable GCT with measurable disease. Comparison with previous studies is hampered by a lack of standardized response evaluation in the majority of studies. Given the toxicity of platinum-based chemotherapy, administering this treatment should be a well-considered decision.
INTRODUCTION

Granulosa cell tumors (GCTs) were first described by Rokitansky as early as 1859. They belong to the group of sex cord-stromal tumors of the ovary and account for 70% of all sex-cord stromal tumors and for 2% to 5% of all ovarian malignancies. The incidence varies between 0.6 and 1.7 cases per 100,000 women per year. In the Netherlands, every year approximately 50 new patients are diagnosed with a GCT. The majority of patients with a GCT present in early stage disease, limited to the ovary, with an excellent short term survival rate. However, long term survival rates drop to 67% 20-year survival rate and a global mortality of 30% to 35%, indicating the potential for late relapse and death. In patients with irresectable advanced-stage disease, platinum-based chemotherapy is commonly used. The Gynecologic Oncology Group is currently conducting a randomized phase 2 trial of BEP (bleomycin, etoposide, and cisplatin) versus the combination of paclitaxel and carboplatin for patients with newly diagnosed and chemotherapy-naive recurrent metastatic sex cord-stromal tumors of the ovary. Although the results of a prospective study showed that 50% to 70% of patients remained progression-free for a long time period after chemotherapy, a comparison with a group that did not receive chemotherapy was not performed. Many other studies claim favorable survival results after chemotherapy but it is difficult to assess the objective response rates from these, predominantly retrospective, case series. Furthermore, drug-related toxic deaths are regularly described in patients with a GCT, up to 2 deaths in 8 patients. The favorable survival results must be seen in the context of a slowly progressing tumor, even when recurrent disease is clinically present.

To assess the objective response rate of chemotherapy in chemotherapy-naive patients with a measurable GCT, the present study was undertaken. In addition, a critical appraisal of the data on the effectiveness of chemotherapy in the treatment of a GCT was performed.

MATERIALS AND METHODS

All patients diagnosed with a GCT between 1968 and 2011 were identified from tumor registry databases of the Center for Gynecologic Oncology Amsterdam, which consists of 3 referral hospitals for gynecologic oncology, and were evaluated for eligibility. Patients were included if they had a histopathologically proven GCT and had been treated with chemotherapy. Only chemotherapy-naive patients were included. Of special interest were the patients with either an incompletely resected GCT at surgery or with a recurrence diagnosed by imaging, measured before and after chemotherapy.
Patients who had received prior radiation therapy were included. The medical records and pathology reports of all patients were reviewed by the first author (H.S.v.M). The following data were retrieved from the medical records: known fertility problems, parity, smoking, alcohol use, medication use, symptoms at presentation, treatment, residual disease, stage, follow-up, recurrence, treatment of recurrence, follow-up of recurrence, and last follow-up status. The pathology reports were reviewed to validate the diagnosis of GCT.

Main outcome was response according to Response Evaluation Criteria in Solid Tumor (RECIST) criteria. These data were collected on the basis of the official radiology reports. A complete response to chemotherapy was defined as a disappearance of all target lesions. A partial response was defined as a decrease of 30% or more in the sum of the longest diameter of target lesions. Progressive disease was defined as a 20% or greater increase in the sum of the longest diameter of target lesions. Stable disease was defined as disease not meeting any of the above mentioned criteria, meaning progressive disease of less than 20% or response of less than 30% in the sum of the longest diameter of target lesions. Progression-free survival (PFS) was defined as the time from the start of chemotherapy to the time of clinical or radiographic evidence of disease progression, death as a result of any cause, or last contact, with events defined as progressive disease or death. Similarly, overall survival (OS) was defined as time from the start of chemotherapy to death from any cause, or last contact, with event defined as death. Follow-up time was defined as the time from diagnosis to death of any cause or last contact. Status of the patient was defined as death from GCT disease, death of intercurrent disease with or without GCT, alive with GCT disease at last follow-up, or no evidence of disease at last follow-up. Statistical analysis was performed using IBM SPSS for windows (version 19.0, IBM Corp., Armonk, NY). Descriptive statistics were calculated for all patients. For PFS and OS, a Kaplan-Meier analysis was performed. Patients were censored at the end of the follow-up period.

A search of the literature in the English language of all previously published cases of chemotherapy in the treatment of GCT was performed by 2 reviewers (H.S.v.M., J.v.d.V.) in MEDLINE through PubMed, from inception to the August 19, 2013. In addition, bibliographies of relevant reviews were searched. The terms in the search strategy are described in Appendix 1. All titles and abstracts were scrutinized after the initial electronic search. Afterward, selected studies were fully reviewed. Studies were included if they met the predefined criteria: English language, a minimum of 5 chemotherapy-naive patients, only adult GCTs or granulosa theca cell tumors (GTCTs), and only chemotherapy of measurable disease (i.e. adjuvant treatment was excluded) with response to chemotherapy described. The following parameters were collected from each article: prospective or retrospective study; histology of tumors; International
Effectiveness of chemotherapy in GCT

Federation of Gynecology and Obstetrics staging (I-IV); number of patients receiving chemotherapy; type of primary treatment (unilateral/bilateral salpingo-oophorectomy/hysterectomy); type of chemotherapy (BEP/other); chemotherapy for primary, residual or recurrent disease; response to chemotherapy (complete/partial/stable/progressive); method of measuring response (radiology/clinical/pathological/surgical); toxic deaths (yes/no); duration of follow-up (in months); recurrent disease (yes/no); and status at last follow-up. The status of the patient was defined as death of disease, death of intercurrent disease with or without disease, alive with disease at last follow-up, or no evidence of disease at last follow-up. Data extraction was done independently and in duplicate by 2 reviewers (H.S.v.M., J.v.d.V.). Main outcome was the response rate to chemotherapy. For this review, descriptive as well as pooled analyses of the main outcome measure were performed. Confidence intervals (CIs) for response rates were calculated.

RESULTS

Cohort Study

Ninety-one patients with a GCT diagnosis were registered in the databases of the Center for Gynecologic Oncology Amsterdam between 1968 until 2011. After reviewing the medical records, radiology reports, and pathology reports, 64 patients were excluded for various reasons (Figure 1).

The remaining 27 patients received chemotherapy. Nine of these patients had combination chemotherapy (BEP) for recurrent disease that was measured before and after treatment with chemotherapy. The characteristics of these 9 patients and their outcomes are reported in Table 1. The median age at diagnosis of these 9 patients was 47 years (range, 33-67 years). Five (56%) of 9 patients received chemotherapy for the first recurrence, 4 patients (44%) received chemotherapy for a second or later recurrence. The 4 patients who received chemotherapy for a second or later recurrence had surgery, radiotherapy, and hormone therapy (patient 2) or only surgery as previous treatments (patient 3, 4 and 9). Seven patients (78%) had stable disease after chemotherapeutic treatment. One patient (11%) had a partial response, and one patient (11%) had a complete response, resulting in an objective response rate of 22% (95% CI, 0-49%).

Median PFS after chemotherapy was 12 months (range, 2-50 months) (Figure 2). Median OS was 50 months (range, 4 to >165 months). The patient with a partial response had a PFS of 25 months, and a survival time of 50 months after BEP was administered. The patient with a complete response on BEP was disease-free for 12 months and survived for 33 months. Five of the 9 patients (56%) were alive at last follow-up. Two of them (22%) had no evidence of disease, after they had received additional surgeries following
chemotherapy. Three patients (33%) died of disease, and one patient died of a drug-induced pneumonitis following BEP combination chemotherapy for GCT (Table 1). Another chemotherapy related toxicity comprised bone marrow suppression grade IV (patient 1) for which further treatment was postponed. The median length of follow-up from diagnosis to last date of contact was 124 months (range, 84-506 months).

Figure 1. Participant flow chart. CT indicates chemotherapy; DOD, death of disease; ICD, intercurrent death; AWD, alive with disease; NED, no evidence of disease.

The other 18 patients received chemotherapy as treatment after surgery with or without residual disease but without measurement before and after chemotherapy. Therefore, no objective response rates could be given. Ten of these patients had no macroscopic residual disease after surgery, before chemotherapy (Figure 1). All 10 patients were alive at last follow-up (range, 38-180 months), 3 with and 7 without evidence of disease. Two patients had evidence of macroscopic residual disease after surgery, before chemotherapy. Both patients died of disease after 22 and 23 months. In the remaining 6 patients, it was not clear whether there was any residual disease after surgery, before chemotherapy. Three of these patients died of disease, 2 were alive with evidence of disease, and 1 was alive without evidence of disease at last follow-up (range, 46-170 months) (Figure 1). Assuming that all 6 patients, where it was not stated if there was any
Table 1. Patients with a GCT who received chemotherapy (CT) with macroscopic recurrent disease, measured by imaging before and after chemotherapy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year of diagnosis</th>
<th>Stage</th>
<th>Type of CT</th>
<th>Recurrent disease*</th>
<th>Size of recurrent disease (cm)</th>
<th>Location of recurrent disease</th>
<th>Imaging†</th>
<th>Technique (and year) of imaging</th>
<th>Response</th>
<th>Progression</th>
<th>PFS‡ (months)</th>
<th>OS§ (months)</th>
<th>Statusǁ</th>
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<tbody>
<tr>
<td>1</td>
<td>1999</td>
<td>IA</td>
<td>BEP 4x</td>
<td>1</td>
<td>15</td>
<td>Abdomen and lung</td>
<td>Yes</td>
<td>CT-scan (2x) (2006)</td>
<td>Stable disease</td>
<td>Yes</td>
<td>50</td>
<td>50</td>
<td>DOD</td>
</tr>
<tr>
<td>2</td>
<td>1968</td>
<td>3C</td>
<td>BEP 3x</td>
<td>6</td>
<td>6</td>
<td>Abdomen</td>
<td>Yes</td>
<td>CT-scan (2x) (2010)</td>
<td>Stable disease</td>
<td>Yes</td>
<td>5</td>
<td>24</td>
<td>AWD</td>
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<tr>
<td>3</td>
<td>2002</td>
<td>2A</td>
<td>BEP 4x</td>
<td>3</td>
<td>13</td>
<td>Vagina</td>
<td>Yes</td>
<td>CT-scan (2x) (2008)</td>
<td>Stable disease</td>
<td>Yes</td>
<td>5</td>
<td>28</td>
<td>AWD</td>
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<tr>
<td>4</td>
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<td>NA</td>
<td>BEP 3x</td>
<td>2</td>
<td>7</td>
<td>Abdomen</td>
<td>Yes</td>
<td>CT-scan (2x) (2007)</td>
<td>Stable disease</td>
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<td>3</td>
<td>ICD</td>
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<tr>
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<td>BEP 2x</td>
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<td>17</td>
<td>Abdomen</td>
<td>Yes</td>
<td>CT-scan (2x) (2010)</td>
<td>Stable disease</td>
<td>No</td>
<td>4</td>
<td>4</td>
<td>NED</td>
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<tr>
<td>6</td>
<td>1998</td>
<td>2C</td>
<td>BEP 4x</td>
<td>1</td>
<td>15</td>
<td>Abdomen</td>
<td>No*</td>
<td>CT-scan (1x) (2004)</td>
<td>Partial response</td>
<td>Yes</td>
<td>25</td>
<td>50</td>
<td>AWD</td>
</tr>
<tr>
<td>7</td>
<td>1996</td>
<td>IA</td>
<td>BEP 4x</td>
<td>1</td>
<td>6</td>
<td>Liver and pelvis</td>
<td>Yes</td>
<td>CT-scan (1x) MRI-scan (2000/2001)</td>
<td>Complete response</td>
<td>Yes</td>
<td>12</td>
<td>33</td>
<td>DOD</td>
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<tr>
<td>8</td>
<td>1994</td>
<td>I</td>
<td>BEP 3x</td>
<td>1</td>
<td>11</td>
<td>Liver and pelvis</td>
<td>Yes</td>
<td>CT-scan (2x) (2001)</td>
<td>Stable disease</td>
<td>Yes</td>
<td>2</td>
<td>4</td>
<td>DOD</td>
</tr>
<tr>
<td>9</td>
<td>1989</td>
<td>NA</td>
<td>BEP 2x</td>
<td>2</td>
<td>NA</td>
<td>Abdomen</td>
<td>Yes</td>
<td>CT-scan (2x) (1997)</td>
<td>Stable disease</td>
<td>Yes</td>
<td>40</td>
<td>165</td>
<td>NED</td>
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</table>

*Number of recurrences until BEP was administered. †Imaging performed before and after chemotherapy. ‡Progression free survival (PFS) in months from start of chemotherapy until progression of disease or last date of follow up. §Overall survival (OS) in months from start of chemotherapy until death or last date of follow-up. ¶Status: Patient status at last follow-up. *Computed Tomography scan. ‡Computed Tomography scan only before surgery, and one after surgery + chemotherapy. Whether the result of the total tumor regression was from surgery or chemotherapy could not be decided, but metastases decreased within the liver and spleen. These were lesions that surgery could not reach, and therefore the cause of the decrease must have been the chemotherapy. **Partial response after surgery + chemotherapy but after chemotherapy response of all non-operated lesions.
residual disease after surgery, did indeed have residual disease, a total of 8 patients had residual disease, of which 1 (13%) showed no evidence of disease in the follow-up after surgery and chemotherapy. The latter patient was disease-free for 31 months after BEP treatment, with a total follow-up time of 170 months.

Figure 2. Progression-free survival of patients that received BEP chemotherapy for recurrent GCT. Time is given from the start of the chemotherapy until progression, last date of follow-up, or death.

Literature review

The search strategy yielded 354 articles that were screened by title and abstract (references available on request) and when of interest fully reviewed. In total, 14 studies met the inclusion criteria. Exclusion criteria were non-English language, inclusion of less than 5 patients receiving chemotherapy, no distinction possible between GCTs or GTCTs and tumors of other histology, only data available on juvenile GCTs, no chemotherapy, only adjuvant chemotherapy, second-line chemotherapy, no new data (reviews), or no response evaluation possible of chemotherapeutic treatment because other treatments like surgery or radiotherapy were also given at the same time.

Including the present study, 15 studies were included after full review and application of exclusion criteria. In these studies, data on 224 patients were available. The median number of cases studied was 13, ranging from 5 to 39 patients. Follow-up time ranged from 1 to 165 months. In 5 studies, the follow-up period was not mentioned; in 1 study, it was not mentioned for all patients. Eight studies were performed retrospectively, and 6 were performed prospectively, and in 1 study, it was not clear whether it was performed prospectively or retrospectively (Table 2).
Type of chemotherapy was available for all patients. The combination of BEP was prescribed in 71 patients. The combination of cisplatin, vinblastine and bleomycin (PVB) and the combination of cyclophosphamide, doxorubicine and cisplatin (CAP) were given in 37 and 19 patients, respectively. In 106 patients, chemotherapy was given for recurrent disease. In 3 patients, chemotherapy was given as primary treatment for advanced disease, in 46 for residual disease and in 69 patients, it was not stated whether it was given as primary treatment or for residual or recurrent disease. The response evaluation was based on imaging in 86 cases. In 36 patients, response was evaluated by clinical judgment, in 17 surgicopathologically, and in 15 patients, it was not clear whether response was evaluated by imaging or surgicopathologically. The method of response evaluation was not stated in 70 patients. In total, 6 toxic deaths occurred in 164 patients (4%) for whom these data were available (Table 2).

Response to chemotherapy was available in 218 patients. In 58 (26%) of the 224 patients, a complete response was documented. In 55 patients (25%), a partial response was observed. Therefore, the pooled estimate of the response rate was 50% (95% CI, 44-57%) (Table 3). In 43 patients (19%), stable disease was observed, and in 41 (18%), progression of disease was observed. In 21 patients (11%), there was no response, but it was unclear whether disease was stable or progressive after chemotherapeutic treatment. At last follow-up, 35 patients had no evidence of disease, of which 21 had had a complete response to chemotherapy, 5 had had a partial response, 2 had had stable disease after chemotherapy, and in 7 patients, this was not clear. Thirty-eight patients were alive with disease, 8 had died of intercurrent causes, and 43 had died of disease. In 100 patients, the status at last follow-up was not stated.
### Table 2. Literature review of the effectiveness of first-line chemotherapy (CT).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>P/R</th>
<th>n</th>
<th>Type of CT</th>
<th>Prim/Res/Rec</th>
<th>Resp, %</th>
<th>Method of resp</th>
<th>Toxic deaths</th>
<th>Follow-up, mo</th>
<th>Status</th>
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<tr>
<td>Schwartz and Smith$^{28}$</td>
<td>1976</td>
<td>R</td>
<td>15</td>
<td>9xAl, 4xT, 2xACFC</td>
<td>9xNA, 6xRec</td>
<td>2xCR (AcFC) (13), 2xPR (13), 11xSD or PD (73)</td>
<td>14xCLI, 1xSur</td>
<td>NA</td>
<td>NA</td>
<td>2xNED, 13xNA</td>
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<tr>
<td>Neville et al$^{19}$</td>
<td>1984</td>
<td>R</td>
<td>7</td>
<td>1xC, 2xF, 1xM, 1xPH, 2xCMFVc</td>
<td>7xRec</td>
<td>2xCR (29), 1xPR (14), 4xSD or PD (57)</td>
<td>7xCLI</td>
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<td>12 (C), 36 (M), 5xNA</td>
<td>2xNED (C&amp;M), 5xNA</td>
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<td>Colombo et al$^{12}$</td>
<td>1986</td>
<td>P</td>
<td>8</td>
<td>8xPVB</td>
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<td>4xCR (50), 2xPR (25), 2xSD or PD (25)</td>
<td>4xCLI, 4xSur</td>
<td>2/8</td>
<td>2-34</td>
<td>4xNED, 2xCD, 2xDOD</td>
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<tr>
<td>Gershenson et al$^{14}$</td>
<td>1987</td>
<td>P</td>
<td>5</td>
<td>5xCAP</td>
<td>2xRes, 3xRec</td>
<td>2xCR (40), 1xPR (20), 1xSD (20), 1xPD (20)</td>
<td>3xSur, 1xSU or CLI, 1xCLI</td>
<td>0/5</td>
<td>4-48</td>
<td>3xNED, 2xDOD</td>
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<td>Zambetti et al$^{31}$</td>
<td>1990</td>
<td>NA</td>
<td>7</td>
<td>7xPVB</td>
<td>3xRes, 4xRec</td>
<td>3xCR (43), 1xPR (14), 2xPD (29), 1xNA (14)</td>
<td>6xCLI, 1xSur</td>
<td>1/7</td>
<td>1-26</td>
<td>3xNED, 2xAWD, 1xCD, 1xDOD</td>
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<tr>
<td>Gershenson et al$^{14}$</td>
<td>1996</td>
<td>P</td>
<td>5</td>
<td>5xBEP</td>
<td>2xRes, 3xRec</td>
<td>2xCR (40), 3xPR (60)</td>
<td>1xSU, 4xCLI</td>
<td>0/5</td>
<td>14-80</td>
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<th>Authors</th>
<th>Year</th>
<th>P/R</th>
<th>n</th>
<th>Type of CT</th>
<th>Prim/Res/Rec</th>
<th>Resp, %</th>
<th>Method of resp</th>
<th>Toxic deaths</th>
<th>Follow-up, mo</th>
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<tr>
<td>Savage et al27</td>
<td>1998</td>
<td>R</td>
<td>22</td>
<td>5xPVB, 1xP, 1xCAP, 3xBEP, 6xP, 2xCa, 2xPCh, 1xCaI, 1xPV</td>
<td>22xPrim or Res</td>
<td>2xCR (9), 6xPR (27), 14xPD (64)</td>
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<td>NA</td>
<td>NA</td>
<td>22xNA</td>
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<td>Pecorelli et al23</td>
<td>1999</td>
<td>P</td>
<td>25++</td>
<td>25xPVB</td>
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<td>Homesley et al8</td>
<td>1999</td>
<td>P</td>
<td>25**</td>
<td>25xBEP</td>
<td>25xNA</td>
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<td>Al-Badawi et al9</td>
<td>2002</td>
<td>R</td>
<td>10</td>
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<td>NA</td>
<td>3-82</td>
<td>1xAWD, 9xDOD</td>
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<td>Uygun et al30</td>
<td>2003</td>
<td>R</td>
<td>14</td>
<td>14xCAP</td>
<td>14xRes</td>
<td>5xCR (36), 5xPR (36), 4xSD or PD (29)</td>
<td>14xRad or Sur</td>
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<th>Type of CT</th>
<th>Prim/Res/Rec</th>
<th>Resp, %</th>
<th>Method of resp</th>
<th>Toxic deaths</th>
<th>Follow-up, mo</th>
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<td>Brown et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>2005</td>
<td>R</td>
<td>39&lt;sup&gt;‡‡&lt;/sup&gt;</td>
<td>8xBEP, 2xPPac, 13xCaPac, 14xPac, 2xDoc, 1xPPacD, 1xDocC&lt;sup&gt;‡&lt;/sup&gt;</td>
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<td>6xCR, 12xPR, 6xSD, 14xPD, 1xNA</td>
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<td>Pectasides et al&lt;sup&gt;25&lt;/sup&gt;</td>
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<td>R</td>
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<td>11xCAP or PEPc, 1xBEP, 1xEEpP</td>
<td>13xPrim or Rec</td>
<td>6xCR (46), 1xPR (8), 4xSD (31), 2xPD (15)</td>
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<td>P</td>
<td>20&lt;sup&gt;ǁǁ&lt;/sup&gt;</td>
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<td>5xRes, 15xRec</td>
<td>9xCR (45), 9xPR (45), 1xSD (5), 1xPD (5)</td>
<td>20xRad</td>
<td>0/20</td>
<td>3-112</td>
<td>9xNED, 3xAWD, 7xDOD, 1xNA</td>
</tr>
<tr>
<td>Van Meurs et al (this study)</td>
<td>2013</td>
<td>R</td>
<td>9</td>
<td>9xBEP</td>
<td>9xRec</td>
<td>1xCR (11), 1xPR (11), 7xSD (78)</td>
<td>9xRad</td>
<td>1/9</td>
<td>3-165</td>
<td>2xNED, 3xAWD, 1xICD, 3xDOD</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>224</td>
<td>6xP, 8xR, 1xNA</td>
<td>58xCR (26), 55xPR (25), 43xSD (19), 41xPD (18), 21xSD or PD (9), 6xNA (3)</td>
<td>6/164</td>
<td>35xNED, 38xAWD, 8xICD, 43xDOD, 100xNA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effectiveness of chemotherapy in GCT

*P/R: Prospective or retrospective study.
†n: Number of evaluable patients receiving chemotherapy.
Type of CT: C indicates cyclophosphamide; Al, alkeran; T, triethylenephosphoramide; Ac, actinomycin-D; F, 5-fluorouracil; M, melphalan; P, cisplatin; H, hexamethylmelamine; Vc, vincristine; V, vinblastine; B, bleomycin; Ad, adriamycin; A, doxorubicin; Ch, chlorambucil; Ep, epirubicin; Mt, methotrexate; Ca, carboplatin; I, ifosfamide; E, etoposide; Pac, paclitaxel; Doc, docetaxel.
Prim/res/rec: chemotherapy administered for primary, residual or recurrent disease.
Resp: response to chemotherapy (CR indicates complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available).
Method of resp: method of measuring response (Rad indicates radiology; Cli, clinical; Sur, surgicopathological; NA, not available).
Fup: duration of follow-up (in months).
Status: Patient status at last follow-up (NED indicates no evidence of disease; AWD, alive with disease; ICD, intercurrent death; DOD, death of disease).

**Status**: Patient status at last follow-up (NED indicates no evidence of disease; AWD, alive with disease; ICD, intercurrent death; DOD, death of disease).
††Includes granulosa theca cell tumors as well.
‡‡Possibly includes tumors of other histology (no distinction can be made from GCTs).
§§One patient was treated on three separate occasions; therefore, the total number of treatment episodes was 41.
ǁǁIncludes 6 juvenile tumors (no distinction can be made from adult GCTs).

### Table 3. Percentage with response to chemotherapy with 95% confidence interval.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz 1976</td>
<td>4/15</td>
<td>27% (4-49%)</td>
</tr>
<tr>
<td>Neville 1984</td>
<td>3/7</td>
<td>43% (6-80%)</td>
</tr>
<tr>
<td>Colombo 1986</td>
<td>6/8</td>
<td>75% (45-100%)</td>
</tr>
<tr>
<td>Gershenson 1987</td>
<td>3/5</td>
<td>60% (17-100%)</td>
</tr>
<tr>
<td>Zambetti 1990</td>
<td>4/7</td>
<td>57% (20-94%)</td>
</tr>
<tr>
<td>Gershenson 1996</td>
<td>5/5</td>
<td>100% (46-100%)</td>
</tr>
<tr>
<td>Savage 1998</td>
<td>8/22</td>
<td>36% (16-56%)</td>
</tr>
<tr>
<td>Pecorelli 1999</td>
<td>13/25</td>
<td>52% (32-72%)</td>
</tr>
<tr>
<td>Homesley 1999</td>
<td>10/25</td>
<td>40% (21-59%)</td>
</tr>
<tr>
<td>Al-Badawi 2002</td>
<td>2/10</td>
<td>20% (0-45%)</td>
</tr>
<tr>
<td>Uygur 2003</td>
<td>10/14</td>
<td>71% (48-95%)</td>
</tr>
<tr>
<td>Brown 2005</td>
<td>18/39</td>
<td>46% (31-62%)</td>
</tr>
<tr>
<td>Pectasides 2008</td>
<td>7/13</td>
<td>54% (27-80%)</td>
</tr>
<tr>
<td>Pautier 2008</td>
<td>18/20</td>
<td>90% (77-100%)</td>
</tr>
<tr>
<td>van Meurs 2013</td>
<td>2/9</td>
<td>22% (0-49%)</td>
</tr>
</tbody>
</table>

Pooled estimate: 113/224 50% (44-57%)
DISCUSSION

In this case series of combination chemotherapy for advanced and recurrent GCT, the objective response rate to chemotherapy (all BEP) was 22% (95% CI, 0-49%). Published series document response rates to chemotherapy of 50% (range, 20-100%, 95% CI, 44-57%), of which 26% complete and 25% partial response, whereas in 47%, no objective response was found (19% no response, 18% progression of disease, 9% unclear whether stable disease or progression).

The difference between this study and the literature was mainly the well-defined and objective criteria for response used in the current study. Only if disease was examined by imaging before and after chemotherapy treatment a patient could be included. Nonetheless, it has to be noted that because of the long time period of patient inclusion, imaging techniques have changed, and the use of RECIST to all imaging in current study has its limitations as well. Many of the previous studies do not describe the method of measuring response rate or state that response was measured “clinically” without enlarging on what this might entail. There seem to be large differences in the definition of response and the method by which this is analysed, and this does not always follow the RECIST criteria. Often complete responses are described in patients with no measurable or residual disease before chemotherapy was administered.

A response rate of 60% was described in patients with residual disease. However, 4 of the 5 patients in that study only had microscopic disease before start of chemotherapy (Table 2). Furthermore, in some studies, the size of the residual or recurrent tumor before chemotherapy was not described. In 2008 Pautier et al described a high response rate of 90%. It should be noted that the size of the measurable tumors before chemotherapy was not stated for all patients. Moreover, control of ascites was reported as partial response in another study.

Another important point of consideration is the fairly short follow-up time of patients in the majority of studies. Because of the slowly progressing nature of GCTs, this could lead to premature conclusions of longer disease-free or progression-free survival, sometimes without comparing to a group that did not receive chemotherapy. Although Uygun et al showed a response rate of 71%, a difference in survival comparing the chemotherapy group and nonchemotherapy group was not found. Homesley et al described 50% to 70% of patients remaining progression-free, but a second-look surgery was only performed in 38 of the 57 patients, of whom 14 had a negative second-look. It should be noted, however, that before start of chemotherapy, positive peritoneal washings were the only localization of disease in 12 patients. It was not stated whether these patients were part of the 25 evaluable patients.
In our study, 1 patient died as a consequence of chemotherapy treatment for GCT. In total, 6 toxic deaths were described in 164 patients.\textsuperscript{8, 12, 31} As this is a considerable percentage, it might be worthwhile to examine other treatment strategies, such as hormonal and anti-angiogenesis therapy.\textsuperscript{35, 36}

Like most published studies, our sample was small and retrospective. Because of this, the observed response rate, albeit substantially lower than those previously reported, falls well within the confidence limits of all other studies. However, the strict inclusion criteria and response evaluation suggest that these results may closer reflect the actual efficacy of this treatment than existing data. After critical review of the literature, in many studies, high response rates to chemotherapy could be explained by other reasons than the administered chemotherapy. Even in the studies where this could not be explained by other reasons, tumor size before chemotherapy was not given for all patients.\textsuperscript{22-24, 32} In several studies, the results seem overly optimistic and not supported by the data.\textsuperscript{8, 9, 12, 14, 19, 25, 27, 28, 30, 31, 34}

In conclusion, in our study, we found a 22\% response rate after combination chemotherapy with BEP. From our review we conclude that the effectiveness of chemotherapy in the treatment of GCTs has been poorly reported. The reason for the observed low response rate may be the fact that in many literature reports response was not measured according to strict guidelines, such as RECIST criteria. In the present study, we could only show a moderate effectiveness of systemic chemotherapy in patients with measurable disease of GCT. The choice for chemotherapy in patients with residual or recurrent GCT must be individualized, and the marginal benefit must be balanced against possible serious side effects, such as toxic death. It is advisable to perform prospective studies to assess the therapeutic ratio of other regimens than the widely used BEP regimen, either less toxic, possibly single-agent chemotherapy, or hormonal and targeted therapies.

\textbf{Acknowledgements}

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APPENDIX 1

Final search strategy in MEDLINE through PubMed