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

Citation for published version (APA):
Chapter 6

Evaluation of response to hormone therapy in patients with measurable adult granulosa cell tumors of the ovary

H.S. van Meurs
J. van der Velden
M.R. Buist
W.J. van Driel
G.G. Kenter
L.R.C.W. van Lonkhuijzen

Submitted
ABSTRACT

Objective
The aim of this study was to determine the objective response rate to hormone therapy (HT) for patients with an adult granulosa cell tumor (GCT) of the ovary in a consecutive series of patients.

Design
Retrospective cohort.

Setting
Tertiary referral centers in the Netherlands.

Population
Patients with a GCT that were treated with HT.

Methods
All patients treated for adult GCT within the Academic Medical Center (between 1990 and 2013), the Free University (between 1984 and 2013) and the Antoni van Leeuwenhoek Hospital (between 1979 and 2013), together accounting for the Center for Gynecologic Oncology Amsterdam, were identified and their records were screened for HT administration.

Main outcome measures
The main outcome was the objective response rate to HT.

Results
We identified 127 patients with an adult GCT, of which 81 (64%) had a recurrence. Twenty-five of these patients (20%) were treated with hormones, of these 22 had measurable disease at the start of their treatment. Pooled objective response rate to HT was 18% (4/22) (95% Confidence Interval 6-41%). In one patient (4.5%) a complete response and in three (14%) a partial response was described. Fourteen patients (64%) had stable disease and in four patients (18%) disease was progressive.

Conclusions
Although several case reports described good responses to HT in patients with a GCT, we found only a moderate demonstrable effectiveness in this large consecutive series of patients.
INTRODUCTION

Granulosa cell tumors (GCTs) are rare ovarian neoplasms that arise from the sex cord-stromal cells and mostly affect middle aged peri- or postmenopausal women. These tumors can be subdivided into adult (95%) and juvenile (5%) types based on clinical and pathologic features. Stage I disease is generally surgically treated only, either with unilateral salpingo-oophorectomy to preserve fertility or alternatively with a hysterectomy and bilateral salpingo-oophorectomy. For irresectable advanced stage GCT or recurrent disease various therapeutic strategies have been investigated. Chemotherapy and radiotherapy are frequently administered, but often do not lead to responses and are associated with morbidity. Therefore less toxic treatments with a higher response rate are required.

GCTs are hormonally active estrogen producing tumors. Around 6% of all patients with a GCT suffer from concurrent endometrial cancer and 26% from concurrent endometrial hyperplasia. Moreover the majority of tumors express hormone receptors. Therefore, hormone therapy (HT) has been investigated as a potential therapeutic regimen. To our knowledge, possibly due to the rarity of the disease, only case reports and small patient series of up to six patients have been described. Several hormonal therapies, such as medroxyprogesterone acetate and aromatase inhibitors, have been described for the treatment of GCT. These small studies describe good responses in general, but as we described in our recently published systematic review it is not known to what extent these results are biased. Possibly only patients with favorable results are selected for inclusion in case reports and case reports that present favorable results could be more likely to be published. It also remains unclear how physicians select those patients whom they treat with HT. As a result HT could appear to be of greater importance than truly is the case. No data are currently available on the response rate to HT in a larger number of patients.

It is necessary to determine the response rate to HT in a larger cohort rather than in case series only. Therefore, in this study we aimed to describe the objective response rate to HT in patients with measurable advanced or recurrent ovarian GCT in a series of consecutive patients.
METHODS

All patients who were primarily treated for adult GCT or referred for surgical treatment of recurrent disease within the Academic Medical Center (between 1990 and 2013), the Free University (between 1984 and 2013) and the Antoni van Leeuwenhoek Hospital (between 1979 and 2013), together accounting for the Center for Gynecologic Oncology Amsterdam, were identified from the PALGA database (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief). The PALGA database is a nationwide network and registry of histopathology and cytopathology in the Netherlands, in which all pathology reports are electronically stored. These patients were cross-checked with the hospital databases. To assure the diagnosis of GCT the pathology reports were reviewed. This study was evaluated by the Regional Ethics Committee and was exempted from approval under Dutch Law (Medical Research Involving Human Subjects Act). Subsequently their records were screened for HT administration. All patients with a GCT that received HT for measurable disease were included in this study. We reviewed the medical records of these patients and retrieved the following data: age at diagnosis; symptoms at presentation, International Federation of Gynecology and Obstetrics stage, earlier treatment, moment of HT administration, reason for HT, duration of HT, estrogen and progesterone receptor status if examined, type and dose of treatment, response to treatment, how response was ascertained and after which time interval, moment of therapy discontinuation, and disease status at last follow-up visit.

The objective response to HT was the primary outcome measure, defined as the proportion of patients whose best overall response to hormone therapy was either complete response or partial response. Response rate was ascertained using the following criteria: a disappearance of all target lesions was defined as a complete response to hormone therapy. A decrease of 30% or more in the sum of the longest diameter of target lesions was defined as a partial response. A 20% or greater increase in the sum of the longest diameter of target lesions was defined as progressive disease. Disease not meeting any of the previously mentioned criteria was defined as stable disease, meaning less than 20% of progressive disease or less than 30% of response of in the sum of the longest diameter of target lesions. If these criteria could not be applied the response rate as described in the patient file based on imaging, inhibin level and/or clinical assessment was used as an alternative. If a patient was treated with multiple sequential HT only the HT with the maximum response was included for analysis.

The time from the start of HT to the time of clinical or radiographic evidence of disease progression, death as a result of GCT disease or last contact was defined as progression free survival (PFS), with events defined as progressive disease or death of GCT. Time
from the start of HT to death from GCT disease, or last contact, was defined as disease specific survival (DSS), with event defined as death from GCT. At the end of the follow-up period or if a patient died of intercurrent disease patients were censored. Death from GCT disease, death of intercurrent disease with or without GCT, alive with GCT disease, or no evidence of disease was the disease status of the patient at last follow-up. Using IBM SPSS for Windows (version 20.0, IBM Corp., Armonk, NY) the statistical analysis was performed. Kaplan-Meier curves were created for PFS and DSS.

RESULTS

We identified 127 patients with an adult GCT of the ovary. These patients were also described in previously published studies.\textsuperscript{4,6,24} Eighty-one (64%) of these patients suffered from recurrent disease. Hormone therapy was administered in 25 (20%) of the 127 patients with an adult GCT. In three patients, hormones were only administered as adjuvant treatment without the presence of measurable GCT disease. In the remaining 22 patients response to HT could be evaluated.

Median age at diagnosis of the 22 patients with HT for measurable disease was 46 years (IQR 37-60). Medical history was positive for breast cancer in three patients (13.6%) and one patient had been diagnosed with uterine cancer. Initial (clinical) International Federation of Gynecology and Obstetrics stage was I in 11 patients, II in five, III in four, IV in one and unknown in one patient.

The characteristics of these 22 patients, the type of HT administered and the response to HT on measurable GCT disease are presented in Table 1. Hormone receptor status was examined in four of the 22 evaluable patients; the progesterone receptor status in four patients and in two of these the estrogen receptor status was examined as well. Progesterone receptor status was positive in all four examined patients (cases 10,12,16 and 19, Table 1). Estrogen receptor status was negative in both examined patients (cases 12 and 16, Table 1). Maximum response was stable disease in three of these patients and progressive disease in one (case 16, Table 1).
Table 1. Characteristics and responses of all patients with hormone therapy on measurable disease.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at diagnosis</th>
<th>Initial stage</th>
<th>Prior treatment</th>
<th>Moment of HT</th>
<th>Reason for HT</th>
<th>Type of HT</th>
<th>Dose of HT</th>
<th>Response</th>
<th>Mode of response</th>
<th>Duration of HT (M)</th>
<th>PFS (M)</th>
<th>DSS (M)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>IV</td>
<td>Sx+CT+RT</td>
<td>P</td>
<td>Residue</td>
<td>MPA</td>
<td>NA</td>
<td>PR</td>
<td>Clinical</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>DOD</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>IIC</td>
<td>Sx(3x)+RT+CT</td>
<td>R3</td>
<td>Residue</td>
<td>Tamoxifen</td>
<td>100 mg t.i.d</td>
<td>SD</td>
<td>Response criteria</td>
<td>2</td>
<td>2</td>
<td>18</td>
<td>DOD</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>IIC</td>
<td>Sx(2x)+RT+CT(2x)</td>
<td>R2</td>
<td>Residue</td>
<td>Tamoxifen</td>
<td>40 mg q.d.</td>
<td>PD</td>
<td>Marker</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>DOD</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>IA</td>
<td>Sx(4x)+CT</td>
<td>R4</td>
<td>Marker increase</td>
<td>Megestrol Acetate</td>
<td>160 mg q.d.</td>
<td>CR</td>
<td>Marker</td>
<td>34+</td>
<td>34+</td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>5a</td>
<td>60</td>
<td>IIA</td>
<td>Sx(4x)+RT(2x)</td>
<td>R5</td>
<td>Prim for R5</td>
<td>Tamoxifen</td>
<td>40 mg q.d.</td>
<td>SD</td>
<td>Response criteria</td>
<td>7</td>
<td>7</td>
<td>26+</td>
<td>ICD (withD)</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>IIA</td>
<td>Sx(4x)+RT(2x)+HT</td>
<td>R5</td>
<td>Residue</td>
<td>Megestrol Acetate</td>
<td>160 mg q.d.</td>
<td>SD</td>
<td>Response criteria</td>
<td>19</td>
<td>19+</td>
<td>19+</td>
<td>ICD (withD)</td>
</tr>
<tr>
<td>6a</td>
<td>32</td>
<td>IA</td>
<td>Sx(5x)+RT(2x)</td>
<td>R6</td>
<td>Prim for R6</td>
<td>Tamoxifen</td>
<td>20 mg b.i.d</td>
<td>PD</td>
<td>Response criteria</td>
<td>5</td>
<td>4</td>
<td>44</td>
<td>DOD</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>IA</td>
<td>Sx(5x)+RT(2x)+HT+CT</td>
<td>R6</td>
<td>Residue</td>
<td>Megestrol Acetate</td>
<td>NA</td>
<td>SD</td>
<td>Response criteria</td>
<td>3</td>
<td>3</td>
<td>27</td>
<td>DOD</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>IC</td>
<td>Sx(3x)</td>
<td>R2</td>
<td>Prim for R2</td>
<td>Megestrol Acetate</td>
<td>160 mg q.d.</td>
<td>PR</td>
<td>Marker</td>
<td>10</td>
<td>10</td>
<td>15+</td>
<td>AWD</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>IIB</td>
<td>Sx</td>
<td>R1</td>
<td>Prim for R1</td>
<td>Megestrol Acetate</td>
<td>160 mg q.d.</td>
<td>SD</td>
<td>Response criteria</td>
<td>Ongoing</td>
<td>7+</td>
<td>7+</td>
<td>AWD</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>IA</td>
<td>Sx(5x)+RT</td>
<td>R5</td>
<td>Prim for R5</td>
<td>Letrozole</td>
<td>2,5 mg q.d.</td>
<td>PD</td>
<td>Response criteria</td>
<td>3</td>
<td>3</td>
<td>11+</td>
<td>ICD (withD)</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>IIB</td>
<td>Sx(3x)</td>
<td>R3</td>
<td>Prim for R3</td>
<td>Megestrol Acetate</td>
<td>160 mg q.d.</td>
<td>SD</td>
<td>Response criteria</td>
<td>Ongoing</td>
<td>4+</td>
<td>4+</td>
<td>AWD</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>IA</td>
<td>Sx(3x)</td>
<td>R3</td>
<td>Prim for R3</td>
<td>Letrozole</td>
<td>2,5 mg q.d.</td>
<td>SD</td>
<td>Response criteria</td>
<td>Ongoing</td>
<td>9</td>
<td>29+</td>
<td>NED</td>
</tr>
<tr>
<td>12</td>
<td>38</td>
<td>IC</td>
<td>Sx(6x)+CT(4x)</td>
<td>R6</td>
<td>Residue</td>
<td>Aromatase Inhibitor</td>
<td>NA</td>
<td>SD</td>
<td>Imaging</td>
<td>3</td>
<td>4</td>
<td>17+</td>
<td>AWD</td>
</tr>
<tr>
<td>13</td>
<td>31</td>
<td>IC</td>
<td>Sx(4x)+CT(3x)+RT</td>
<td>R5</td>
<td>Residue</td>
<td>Tamoxifen</td>
<td>40 mg q.d.</td>
<td>PR</td>
<td>Clinical</td>
<td>5</td>
<td>5</td>
<td>13</td>
<td>DOD</td>
</tr>
<tr>
<td>Case</td>
<td>Age at diagnosis</td>
<td>Initial stage</td>
<td>Prior treatment</td>
<td>Moment of HT</td>
<td>Reason for HT</td>
<td>Type of HT</td>
<td>Dose of HT</td>
<td>Response</td>
<td>Mode of response</td>
<td>Duration of HT (M)</td>
<td>PFS (M)</td>
<td>DSS (M)</td>
<td>Status</td>
</tr>
<tr>
<td>------</td>
<td>-----------------</td>
<td>--------------</td>
<td>----------------</td>
<td>--------------</td>
<td>--------------</td>
<td>------------</td>
<td>------------</td>
<td>----------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>---------</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>13a</td>
<td>31</td>
<td>IC</td>
<td>Sx(4x)+CT(3x)+RT+HT</td>
<td>R5</td>
<td>Residue</td>
<td>Megestrol Acetate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>160 mg q.d.</td>
<td>PD</td>
<td>Imaging</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>DOD</td>
</tr>
<tr>
<td>13a</td>
<td>31</td>
<td>IC</td>
<td>Sx(4x)+CT(3x)+RT+HT(2x)</td>
<td>R5</td>
<td>Residue</td>
<td>Goserelin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA</td>
<td>PD</td>
<td>Imaging</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>DOD</td>
</tr>
<tr>
<td>14</td>
<td>43</td>
<td>IIIC</td>
<td>Sx(4x)</td>
<td>R4</td>
<td>Prim for R4</td>
<td>Letrozole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2,5 mg q.d.</td>
<td>SD</td>
<td>Imaging</td>
<td>14</td>
<td>44+</td>
<td>44+</td>
<td>AWD</td>
</tr>
<tr>
<td>14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>43</td>
<td>IIIC</td>
<td>Sx(4x)+HT</td>
<td>R4</td>
<td>Residue</td>
<td>Letrozole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NA</td>
<td>SD</td>
<td>Imaging</td>
<td>7</td>
<td>30+</td>
<td>30+</td>
<td>AWD</td>
</tr>
<tr>
<td>15</td>
<td>51</td>
<td>IIIB</td>
<td>Sx(2x)+CT</td>
<td>R2</td>
<td>Prim for R2</td>
<td>Tamoxifen&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
<td>PD</td>
<td>Imaging</td>
<td>2</td>
<td>2</td>
<td>14</td>
<td>DOD</td>
</tr>
<tr>
<td>16</td>
<td>69</td>
<td>IC</td>
<td>Sx(3x)</td>
<td>R3</td>
<td>Prim for R3</td>
<td>Tamoxifen&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1/4 wk sc</td>
<td>PD</td>
<td>Imaging</td>
<td>8</td>
<td>8</td>
<td>11+</td>
<td>AWD</td>
</tr>
<tr>
<td>16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69</td>
<td>IC</td>
<td>Sx(3x)+HT</td>
<td>R3</td>
<td>Residue</td>
<td>Letrozole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2,5 mg q.d.</td>
<td>PD</td>
<td>Imaging</td>
<td>3</td>
<td>3</td>
<td>3+</td>
<td>AWD</td>
</tr>
<tr>
<td>17</td>
<td>76</td>
<td>NA</td>
<td>Sx(2x)+HT</td>
<td>R1</td>
<td>Residue</td>
<td>Letrozole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2,5 mg q.d.</td>
<td>SD</td>
<td>Marker</td>
<td>13</td>
<td>18</td>
<td>102</td>
<td>DOD</td>
</tr>
<tr>
<td>18</td>
<td>24</td>
<td>IC</td>
<td>Sx(6x)+CT(3x)+RT</td>
<td>R5</td>
<td>Residue</td>
<td>Megestrol Acetate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>160 mg q.d.</td>
<td>SD</td>
<td>Imaging</td>
<td>29</td>
<td>33</td>
<td>73+</td>
<td>AWD</td>
</tr>
<tr>
<td>19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44</td>
<td>IC</td>
<td>Sx(2x)+CT</td>
<td>R2</td>
<td>Prim for R2</td>
<td>Anastrozole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1/4 wk sc</td>
<td>PD</td>
<td>Imaging</td>
<td>5</td>
<td>5</td>
<td>11+</td>
<td>AWD</td>
</tr>
<tr>
<td>19</td>
<td>44</td>
<td>IC</td>
<td>Sx(2x)+CT+HT</td>
<td>R2</td>
<td>Residue</td>
<td>Letrozole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NA</td>
<td>SD</td>
<td>Response criteria</td>
<td>Ongoing</td>
<td>8+</td>
<td>8+</td>
<td>AWD</td>
</tr>
<tr>
<td>20</td>
<td>52</td>
<td>IIIC</td>
<td>Sx(2x)</td>
<td>R2</td>
<td>Prim for R2</td>
<td>Anastrozole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1 mg q.d.</td>
<td>SD</td>
<td>Imaging</td>
<td>5</td>
<td>12+</td>
<td>12+</td>
<td>AWD</td>
</tr>
<tr>
<td>21</td>
<td>38</td>
<td>II</td>
<td>Sx(4x)+CT(5x)+RT</td>
<td>R4</td>
<td>Residue</td>
<td>Goserelin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1/4 wk sc</td>
<td>SD</td>
<td>Imaging</td>
<td>4</td>
<td>53</td>
<td>112</td>
<td>DOD</td>
</tr>
<tr>
<td>22</td>
<td>44</td>
<td>I</td>
<td>Sx(3x)+CT(3x)+RT</td>
<td>R3</td>
<td>Residue</td>
<td>Tamoxifen&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10 mg t.i.d.</td>
<td>SD</td>
<td>NA</td>
<td>5</td>
<td>36</td>
<td>36</td>
<td>DOD</td>
</tr>
</tbody>
</table>

<sup>a</sup>Different hormone therapy leading to less response in the patient described with same case number.

<sup>b</sup>Steroidal progestin.

<sup>c</sup>Selective Estrogen Receptor Modulator (SERM).

<sup>d</sup>Aromatase Inhibitor.

<sup>e</sup>Gonadotropin-Releasing Hormone (GnRH) agonist.

<sup>f</sup>Type of aromatase inhibitor unknown.

HT, hormone therapy; PFS, progression free survival; DSS, disease specific survival; M, month(s); Sx, surgery; CT, chemotherapy; RT, radiotherapy; P, primary disease; R1, first recurrence; R2, second recurrence; R3, third recurrence; R4, fourth recurrence; R5, fifth recurrence; R6, sixth recurrence; Prim, primary treatment; MPA, medroxyprogesterone acetate; sc, subcutaneous; q.d., once a day; b.i.d., two times a day; t.i.d., three times a day; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NED, no evidence of disease; AWD, alive with disease; ICD, intercurrent death; withD, with GCT disease; DOD, dead of disease; NA, not available; n/a, not applicable.
Figure 1. Progression free survival in months of 22 patients after start of hormone therapy for measurable disease.

Figure 2. Disease specific survival in months of 22 patients after start of hormone therapy for measurable disease.
All patients had surgery as primary treatment. Eleven patients were treated with chemotherapy prior to HT and in 10 patients radiotherapy was given before administration of HT. Twenty patients had had a second (n=five), third (n=six), fourth (n=five), fifth (n=two) or sixth (n=two) surgical treatment for GCT recurrence. In one patient HT was administered at primary diagnosis (after receiving surgery, chemotherapy and radiotherapy, case one, Table 1), in two as treatment for first recurrence, in five for second, in five for third, in three for fourth, in four for fifth and in two for sixth recurrent tumor.

Steroidal progestins were administered in nine patients, Selective Estrogen Receptor Modulators (SERM) in eight, Aromatase Inhibitors in 10 and Gonadotropin-Releasing Hormone (GnRH) agonist in two patients. Six patients received multiple HTs. Eighteen percent (4/22) (95% Confidence Interval 6-41%) was the pooled objective response rate. A complete response was observed in one patient (4.5%) (case four, Table 1) and a partial response in three patients (14%) (cases one, seven and 13, Table 1). Fourteen patients (64%) had stable disease and in four patients (18%) disease was progressive.

Median PFS after HT was 10 months (range 2-53) and is shown in Figure 1. Median DSS after HT was 36 months (range 2-112) (Figure 2). For the four patients who responded, PFS was two, five, 10 and 34+ months. The first two died of disease after two and 13 months (cases one and 13, Table 1). They were treated with medroxyprogesterone acetate (MPA) and tamoxifen respectively. The third patient, treated with megestrol acetate, was alive with disease after 15 months (case seven, Table 1). The patient who showed a complete response was also treated with megestrol acetate and had no evidence of disease after 34 months (case four, Table 1). These responses were based on clinical (cases one and 13, Table 1) and marker (cases four and 7, Table 1) evaluation.

DISCUSSION

To determine the response rate to HT in patients with a measurable GCT, we examined a cohort of 22 patients. In these consecutive patients with advanced and recurrent adult GCT, we reported an objective response rate of 18% (95% Confidence Interval 6-41%). The four patients who responded to HT showed a PFS of two, five, 10 and 34+ months. In several earlier studies HT is suggested as a viable treatment option in patients with an ovarian GCT.21

Several mechanisms have been suggested for the inhibition of tumor growth through hormone manipulation in GCTs; either through indirect action on tumors by suppression of gonadotrophins or endogenous steroids, or through direct effects on the tumor by a local mechanism mediated through GCT receptors or a combination of these theories.9
As early as 1970 HT was suggested as a possible treatment option for patients with a GCT. Multiple case reports followed showing generally good responses.\textsuperscript{9, 12, 13, 15-17, 19, 20, 25-27} Some small patient series were published as well, for example Fishman et al reported a series of six patients treated with monthly leuprolide. Response could be evaluated in five of these patients; two had a partial response for 12 and three months and the remaining three patients had stable disease.\textsuperscript{11} Two other reports described a small series of four patients receiving HT. One reported of three complete responses and one partial response on aromatase inhibitors, lasting for 12 to more than 54 months.\textsuperscript{14} Lastly, Kauppila et al described four patients with HT resulting in two partial responses for three months and two therapies that lead to progressive disease.\textsuperscript{28} Recently we have published a systematic review summarizing all reported responses from the literature on HT in patients with a GCT. Pooling the results of all case reports and case series lead to an objective response rate of 71% (95% CI 52-85).\textsuperscript{21}

In this study, we could only show a small benefit of HT in patients with a GCT. This result could possibly be explained by the fact that in nearly all cases HT was administrated as a ‘last resort’ therapy in heavily pre-treated patients who showed progression after all surgical, chemotherapeutic and radiation therapies had failed. Responses could conceivably be better when HT is administered earlier for instance at first recurrence.

Furthermore, we reported a series of consecutive patients with measurable disease, instead of single patients only, therefore providing more accurate information on response in an unselected group of patients. These results probably are a better reflection of the true effect of HT in clinical practice. Prior more positive results as published in small case series have a likelihood of being influenced by selection and/or publication bias, where positive results are more likely to get published than negative results.

Aromatase inhibitors were reported as yielding the most promising results in our review.\textsuperscript{21} Our current results do not support this superiority of aromatase inhibitors; of 10 administrated aromatase inhibitors in the current study seven resulted in stable disease and three in progressive disease.

Hormone receptor status of the tumor was only examined in four patients; all were positive for progesterone receptor and two were negative for estrogen receptors. All had stable or progressive disease as maximum response to HT. Case reports described a complete response, a partial response and a stable disease in estrogen negative and progesterone positive patients.\textsuperscript{9, 27, 29} No unambiguous conclusions can be drawn from these inconsistent outcomes on hormone receptor positivity, because of the small patient numbers. Hormone receptor status was largely unexplored in our cohort as well as in most previous reports on hormone therapy in GCT. Since some studies suggest that a higher steroid receptor expression leads to a better response to HT, this needs further attention in future studies.\textsuperscript{30}
HT has the advantage of showing limited side effects. Consequently, when responses would be comparable to for example chemotherapy, HT could be considered as the primary medical treatment to be given, due to its lower toxicity. It is therefore important to study the response rate of HT more thoroughly in prospective studies, such as the PARAGON trial that is currently recruiting patients.

We showed that 18% of patients had an objective response to HT. It has to be noted though, that the positive responses were ascertained by clinical examination or by a decrease in tumor marker only. None of these responses were confirmed by the response criteria and they lasted only short, for two, five and 10 months only. In one patient response was complete for more than 34 months. However, if responses to HT are seen in even a small percentage of cases, treatment with hormones prior to less harmful alternatives such as radio- and chemotherapy could be indicated.

The greatest strength of our study is that instead of a case report describing only one or two patients, we describe a number of consecutive patients with a GCT that received HT for measurable residual or recurrent disease. This approach was already suggested by other authors, who stated that although results with HT for GCT seem impressive, no conclusions can be drawn due to the low number of patients and that confirmation in a larger cohort is required.

Due to the long time interval to recurrent disease in patients with a GCT, it is difficult to assess the impact of adjuvant treatment on PFS or DSS. Therefore, to accurately determine response to HT, we evaluated HT on measurable disease by excluding patients that received HT as adjuvant treatment (n=three). Various other studies described responses while HT was administrated as adjuvant treatment only.

Although to our knowledge we describe the largest study ever conducted on HT response in GCT patients, the low number of 22 patients in our study reflects the low incidence of only 0.61 cases per 100,000 women per year. Besides the small sample size, its retrospective design represents another limitation of our study.

CONCLUSION

In conclusion, in the treatment of patients with an ovarian GCT, experience with hormonal approaches is limited. Although HT seems an attractive treatment option in several case reports, we showed only a minimal benefit in this cohort study of consecutive GCT patients. Future studies will have to provide evidence for the effectiveness of endocrine therapy in patients with a GCT to draw final conclusions.
REFERENCES


