Gynecologic Oncology 142 (2016) 452–457

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Prognostic significance of an early decline in serum alpha-fetoprotein during chemotherapy for ovarian yolk sac tumors

Thibault de la Motte Rouge [a,*], Patricia Pautier [b], Catherine Genestie [c], Annie Rey [d], Sébastien Gouy [e], Alexandra Leary [b], Christine Haie-Meder [f], Pierre Kerbrat [a], Stéphane Culine [g], Karim Fizazi [b], Catherine Lhommé [b]

[a] Department of Medical Oncology, Centre Eugène Marquis, Av de la bataille Flandres-Dunkerque, CS 44229, F-35042 Rennes, France
[b] Department of Cancer Medicine, Institut Gustave-Roussy, 114 rue Edouard Vaillant, F-94805 Villejuif, France
[c] Department of Biopathology, Institut Gustave-Roussy, 114 rue Edouard Vaillant, F-94805 Villejuif, France
[d] Department of Biostatistics, Institut Gustave-Roussy, 114 rue Edouard Vaillant, F-94805 Villejuif, France
[e] Department of Surgery, Institut Gustave-Roussy, 114 rue Edouard Vaillant, F-94805 Villejuif, France
[f] Department of Radiotherapy, Institut Gustave-Roussy, 114 rue Edouard Vaillant, F-94805 Villejuif, France
[g] Department of Medical Oncology, CHU Hôpital Saint Louis, 1 avenue Claude-Vellefaux, F-75010 Paris, France

HIGHLIGHTS

- Ovarian yolk sac tumors (OYST) belong to ovarian germ cell tumors.
- Elevated serum alpha-fetoprotein (AFP) is one of the hallmarks of OYSTs.
- Following surgery, BEP chemotherapy has become the standard of care in OYSTs.
- Serum AFP decline between baseline and day 21 is an independent prognostic factor.
- This may help to select patients for risk-adapted chemotherapy treatment.

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 2 July 2016
Accepted 4 July 2016
Available online 8 July 2016

Keywords:
Alpha-fetoprotein
BEP
Endodermal sinus tumor
Malignant ovarian germ cell tumor
Chemotherapy
Germ cell tumor

ABSTRACT

Background. The ovarian yolk sac tumor (OYST) is a very rare malignancy arising in young women. Our objective was to determine whether an early decline in serum alpha-fetoprotein (AFP) during chemotherapy has a prognostic impact.

Methods. This retrospective study is based on prospectively recorded OYST cases at Gustave Roussy (Cancer Treatment Center). Survival curves were estimated using the Kaplan-Meier method. The serum AFP decline was calculated with the formula previously developed and validated in male patients with poor prognosis non-seminomatous germ cell tumors. Univariate and multivariate analyses were performed using the log-rank test and logistic regression, respectively.

Results. Data on AFP were available to calculate an early AFP decline in 57 patients. All patients had undergone surgery followed by chemotherapy. The 5-year overall survival (OS) and event-free survival (EFS) rates were 86% (95% CI: 74%–93%) and 84% (95% CI: 73%–91%), respectively. The disease stage, presence of ascites at presentation, use of the BEP regimen, serum AFP half-life and an early AFP decline were significantly predictive factors for OS and EFS in the univariate analysis. The OS rate was 100% and 49% (95% CI: 26%–72%) in patients with a favorable AFP decline and in those with an unfavorable decline, respectively ($p < 0.001$). In the multivariate analysis, only the presence of ascites at diagnosis (RR = 7.3, $p = 0.03$) and an unfavorable early AFP decline (RR = 16.9, $p < 0.01$) were significant negative predictive factors for OS.

Conclusions. An early AFP decline during chemotherapy is an independent prognostic factor in patients with OYSTs.

Conflict of interest statement. No conflict of interest

* Corresponding author at: Centre Eugène Marquis, Av de la bataille Flandres-Dunkerque, CS 44229, F-35042 Rennes, France.
E-mail address: catherine.lhomme@gustaveroussy.fr (C. Lhommé).

http://dx.doi.org/10.1016/j.ygyno.2016.07.005
0090-8258/

1. Introduction

Ovarian yolk sac tumors (OYSTs), also known as endodermal sinus tumors, belong to the group of malignant ovarian germ cell tumors (MOGCTs). This is a very rare disease that occurs in young women. Elevated serum alpha-feto-protein (AFP) and positive staining of AFP in tumors cells assessed by immunochemistry on a pathology sample facilitates the diagnosis [1]. Until the 1990s, OYSTs were associated with a very poor prognosis and most authors agree that YSTs carry the worse prognosis among MOCGTs [2]. Cisplatin-based multi-agent chemotherapy has dramatically improved the prognosis of MOGCTs. More recently, the BEP combination (bleomycin, etoposide, cisplatin) appeared to be the most active combination regimen and was established as the standard of care in MOGCTs [3,4].

We and others recently validated these findings in the specific subset of OYSTs. A substantial majority of patients will be cured after surgery and BEP chemotherapy [5–7]. Despite this very good outcome, the prognosis is poor in some patients who eventually relapse. In OYSTs, early identification of these patients remains challenging, as prognostic factors are lacking in this entity.

Regarding treatment, experience derived from non-seminomatous germ cell tumors (NSGCT) in male patients may help provide greater clinical insight into OYSTs. In poor prognosis NSGCT, an early serum tumor marker decline (AFP and/or hCG) has been demonstrated to predict outcome [8]. This finding was subsequently corroborated in a prospective randomized phase III clinical trial, which also evidenced that an early switch in the chemotherapy regimen for patients with a slow tumor marker decline reduces the risk of progression or death [9]. The same concept also proved valid in patients treated for advanced NSGCT with second-line salvage chemotherapy [10].

Here, we evaluated the prognostic relevance of an early serum AFP decline in OYSTs.

2. Methods

2.1. Patient population

This retrospective study is based on prospectively recorded OYST cases at Gustave-Roussy (Villejuif, France). We previously reported on the outcome of that series comprising 84 patients [6].

To summarize, only postpubertal cases were included as some studies reported that the physiopathology of OYSTs occurring in children and young women could be different [11]. Information concerning all patients was abstracted from the medical records in accordance with local regulations. We included only the 57 patients for whom data on AFP at baseline, prechemotherapy, and at days 18–21 following the 1st chemotherapy cycle were available to calculate an early AFP decline.

2.2. Staging and tumor classification

The International Federation of Gynecology and Obstetrics (FIGO) 2000 staging system for ovarian cancers was used [12]. The histological type was defined according to the WHO classification [13]. Most of the stage I lesions had not been properly assessed according to FIGO recommendations in patients referred after surgery, especially with respect to peritoneal cytology. Stage Ia was therefore defined as a tumor strictly limited to one ovary, with an intact capsule, without ascites and no tumor cells in peritoneal cytology, when available. Stage Ic tumors were strictly limited to one ovary but exhibited capsular rupture or ascites >100 mL or ascites with tumor cells, when available.

2.3. Treatment and tumor response

Most of the patients were referred to Gustave Roussy following initial surgery. In the majority of cases, a single ovarian procedure without staging surgery was performed. In these patients, restaging and secondary surgery were reconsidered only after chemotherapy. An analysis of the surgical reports and postoperative imaging studies helped us evaluate the presence of any residual tumors before starting chemotherapy.

At Gustave Roussy, surgical guidelines changed over time. Initially, radical surgery comprising bilateral salpingo-oophorectomy, hysterectomy, lymphadenectomy and omentectomy, was recommended. Then, given the high rate of cure achieved with BEP chemotherapy, a less invasive surgical procedure was proposed in order to spare fertility whenever possible. Nowadays, in early-stage disease, our national guidelines recommend unilateral salpingo-oophorectomy with peritoneal staging procedures. In advanced disease, a fertility-sparing approach is recommended whenever possible in young women.

Chemotherapy followed standardized international protocols. Before the 1990s, virtually all patients had received a platinum-based combination chemotherapy. Some patients were enrolled in a prospective phase II trial assessing a high-dose of cisplatin combined with vinblastine, bleomycin and etoposide (PVeVB) [14]. Since 1996, BEP has become our standard chemotherapy regimen.

2.4. Early serum AFP decline

The serum AFP decline was calculated with the formula applied at Gustave Roussy in poor prognosis NSGCTs. It is available for free on the website (www.gustaveroussy.fr/calculation-tumor/NSGCT.html). The method used to calculate the AFP decline was previously published [8]. The baseline prechemotherapy and days 18–21 serum AFP level following the 1st chemotherapy cycle are entered in a logarithmic formula which defines a favorable and unfavorable pattern of decreased AFP. The patients were classified into a group with either a favorable or an unfavorable AFP decline.

2.5. Statistical analysis

Survival curves were calculated using the Kaplan-Meier method. OS was calculated from the date of the diagnosis to the time of the last follow-up or death. Event-free survival (EFS) was calculated from the date of the diagnosis to the date of the first event, defined as a relapse, a progressive tumor or death from any cause.

The univariate analysis using the log-rank test investigated potential correlations between survival and patient or disease covariates. To determine the independent prognostic significance of the factors for OS and EFS, a multivariate analysis was conducted using a logistic regression model. Only factors that were significant in the univariate analysis were subsequently incorporated into the multivariate model. A multivariate analysis adjusted on BEP treatment was also conducted.

3. Results

3.1. Patient and disease characteristics

Patient characteristics and treatment modalities are summarized in Table 1. Median follow-up was 66 [3–243] months. The median AFP value was 1040 (2–116,359) ng/mL at baseline prior to start chemotherapy. Most of the patients (42/57) had undergone fertility-sparing surgery. Cisplatin-based chemotherapy had been administered to 56/57 patients and 42/57 patients had received BEP regimen.

3.2. Outcome

The estimated 5-year OS and EFS rates were 86% (95% CI: 74%–93%) and 84% (95% CI: 73%–91%), respectively (Fig. 1).

Progressive disease or recurrence had been observed in 7 patients: 1/1 patient who had not received cisplatin during initial chemotherapy; 3/14 patients who had received cisplatin-based chemotherapy regimens without etoposide and in 3/42 patients who had received the BEP regimen.