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Original Article

Immunomodulatory therapy in refractory/recurrent ovarian cancer

Chao-Yu Chen [a], Chyong-Huey Lai [a], Lan-Yan Yang [b], Yun-Hsin Tang [a], Hung-Hsueh Chou [a], Chee-Jen Chang [c], Cheng-Tao Lin [a,*]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan
[b] Gynecologic Cancer Research Center and Biostatistics and Informatics Unit, Clinical Trial Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[c] Research Center of Clinical Informatics and Medical Statistics, Chang Gung University, Taoyuan, Taiwan

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ABSTRACT

Objective: To investigate the efficacy and toxicity of immunomodulatory therapy (IMT) alone or as an add-on to palliative/salvage chemotherapy in patients with refractory/recurrent epithelial ovarian cancer (EOC).
Materials and methods: We retrospectively analyzed the efficacy and toxicity of IMT in 15 patients with refractory/recurrent EOC who had previously received multiple chemotherapy regimens.
Results: The median age of the patients was 56 years (range, 41–75 years). Three patients were platinum-sensitive, two were platinum-resistant, and the remaining 10 patients were refractory to platinum-based front-line chemotherapy. IMT consisted of picibanil (OK-432) on Day 1, interleukin-2 and/or interferon-α on Day 2 administered by subcutaneous injection (every week or 2-weekly). Five patients never received metronomic oral cyclophosphamide. After IMT, three patients achieved partial remission (PR, lasting for 11 months, ≥ 12 months, and 16 months), and six patients had stable disease (SD). The disease stabilizing rate (PR+SD) was 60% (3/3 in platinum-sensitive and 6/12 in platinum-resistant/refractory patients). The absolute lymphocyte count (ALC) at 1 month after IMT was significantly higher in the PR+SD group (median 1242.0/μL) than in the progression group (median 325.0/μL) ($p = 0.012$). No ≥ Grade 3 toxicities were observed. The median post-IMT survival time was 12 months (range, 2–39 months).
Conclusion: IMT alone or add-on to palliative/salvage chemotherapy for refractory/recurrent EOC achieves a substantial disease stabilizing rate without severe toxicity, which might be a potential option in selected patients. The ALC 1 month after IMT could be an early indicator to disease stabilization.

Introduction

Epithelial ovarian cancer (EOC) is the eighth most common malignancy and the seventh leading cause of cancer-related mortality in women worldwide [1]. In 2009, EOC accounts for 1113 new cases, 438 deaths, and ranks the second lethal gynecologic malignancy in Taiwan [2]. Although EOC is generally diagnosed at an advanced stage, primary cytoreductive surgery followed by platinum-based chemotherapy can ensure the achievement of a complete remission (CR) in 70–80% of patients. Unfortunately, 60–70% of advanced EOC patients will have disease relapse after primary treatment [3–5]. Furthermore, disease progression during first-line treatment is associated with a dismal prognosis.

In general, the response rates of platinum-sensitive patients to second-line chemotherapy are usually > 30%. Conversely, platinum-resistant patients show response rates as low as 10–20% [3,5,6]. In addition, current salvage strategies for patients with refractory/recurrent EOC are not effective and rarely curative. Therefore, novel therapy treatment strategies have been eagerly awaited.

Previous studies demonstrated the clinical usefulness of immunomodulatory therapy (IMT) in several solid malignancies, including lung cancer, hepatocellular carcinoma, prostate cancer, melanoma, and renal cell carcinoma [7]. Because EOC have immunogenic properties [8], the potential usefulness of immunological approaches for the treatment of advanced EOC is attracting

* Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, 5 Fu-Shin Street, Kueishan, Taoyuan 333, Taiwan.
E-mail address: 51424@cgmh.org.tw (C.-T. Lin).

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increasing interest. In addition, the presence of tumor-infiltrating lymphocytes has been shown to predict survival in EOC patients, suggesting the prognostic relevance of immune surveillance mechanisms in the course of this malignancy [9]. Notably, the increase of regulatory T (Treg)-cells in patients with EOC has been associated with a reduced survival [10]. The efficacy and low toxicity of IMT has been observed [8,11,12]. These results prompt us to apply similar approaches in advanced EOC with refractory/recurrent disease.

Penicillin-killed *Streptococcus pyogenes* [OK-432; Toll-like receptor (TLR) 4 agonist] is administered subcutaneously to activate skin Langerhans cells to enhance antigen presenting and upregulation of CD25 expression. OK-432 can trigger dendritic cell (DC) activation via the TLR 4–MD2 signal pathway, inducing DC maturation and linking innate cells and adaptive immune cells in host immunosurveillance [13]. The clinical usefulness of OK-432 for the treatment of lymphangioma, gastric cancer, and lung cancer has been extensively investigated in Japan [13]. Interleukin (IL)-2 can restore the ability of the immune system to produce $CD4^+$ T cells and increase IL-2-induced $CD4^+$ $CD25^+$ ($CD4^+FOXP3^+$) T cells, which can in turn suppress Treg cells [14,15]. IL-2 has been approved in the United States for treating metastatic renal cell carcinoma and metastatic melanoma [16]. Interferons (IFNs) may exhibit important antitumoral and antiangiogenetic effects and induce apoptosis in malignant cells [7]. Type I IFNs (α/β) systemically activate natural killer (NK) cells and support the differentiation, maturation, and migration of DCs [17]. A single administration of cyclophosphamide was shown to deplete $CD4^+CD25^+$ T cells in tumor-bearing animals, delay tumor growth, and cure rats bearing established tumors when followed by an immunotherapy that has no curative effect when administered alone [18].

We therefore hypothesized that cytokine-based therapy in combination with oral metronomic chemotherapy (as a form of IMT) for refractory/recurrent EOC may improve survival. The purpose of this study is to review the efficacy and toxicity obtained in patients treated with IMT alone or add-on to palliative/salvage chemotherapy after failure of front-line treatment in our hospital.

Patients and methods

Patients

This study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital, Taoyuan, Taiwan (100-3902A3). We retrospectively reviewed the medical records of 15 patients with refractory/recurrent advanced EOC who were treated with cytokine-based IMT between December 2004 and January 2013. Inclusion criteria were as follows: (1) age $\leq$ 75 years at the time of diagnosis of ovarian cancer; (2) pathologically-confirmed EOC; (3) initial treatment with surgical cytoreduction and platinum-based chemotherapy; (4) evidence of disease progression during first-line chemotherapy (refractory), or evidence of disease recurrence within 6 months after an initial response to first-line chemotherapy (platinum-resistant), or disease recurrence > 6 months after an initial complete response to first-line chemotherapy (platinum-sensitive) but failed salvage systemic chemotherapy; and (5) use of IMT either alone or as an add-on to chemotherapy.

Immunomodulatory therapy

IMT was performed with the following drugs: OK-432 [5 Klinische Einheit (KE, a unit of OK-432 dose)/vial, Picibanil; Chugai Pharmaceutical Co., Ltd. Tokyo, Japan], IL-2 (18 MIU/vial, Aldesleukin; Chiron B.V., Amsterdam, The Netherlands), peginterferon (PEG-IFN)-α-2a (3 MIU/0.5 mL/syringe, Roferon-A; F. Hoffmann-La Roche Ltd., Basel, Switzerland), or IFN-β-1b [0.3 mg (9.6 MIU)/vial, Betaferon; Novartis Vaccines and Diagnostics, Inc., Emeryville, California, USA]. All of the patients received IMT either with or without metronomic chemotherapy at the physician's discretion. IMT was administered in the hospital by subcutaneous injections. The use of OK-432 and IL-2 has been introduced since December 2004, whereas the administration of IFNs started in September 2006. Patients started IMT with a single agent, and other drugs were subsequently added in patients who did not show severe side effects. After 2011, the IMT regimens evolved into one vial of OK-432 on Day 1, one vial of IL-2, and/or one vial of IFN-α-2a on Day 2 (or Day 2 and Day 3) weekly or 2-weekly. Cytokine agents were discontinued in patients who showed severe chemotherapy-related leukopenia, infections, clinical signs of target organ failure due to disease progression, or who refused to continue IMT. Salvage/palliative chemotherapy was administered after IMT if there was no neutropenia or thrombocytopenia against its use. Metronomic chemotherapy consisted of oral cyclophosphamide 50 mg once per day after salvage/palliative chemotherapy until the next course IMT.

Taiwan Food and Drug Administration approved the use of OK-432 for the treatment of gastrointestinal cancer, head and neck cancer, thyroid cancer, and lung cancer; IL-2 for metastatic renal cell carcinoma and metastatic melanoma; PEG-IFN-α-2a for Kaposi's sarcoma, renal cell carcinoma, hairy cell leukemia, chronic hepatitis B and C, chronic myeloid leukemia, cutaneous T cell lymphoma, and non-Hodgkin's lymphoma [19]. All of the patients were informed about the off-label use of IMT for the treatment of EOC.

Clinical assessment

The patients were classified as sensitive, resistant, or refractory to platinum-based therapy depending on the interval between the initial response and the first relapse [20]. Routine blood counts, liver function tests, renal function test, and serum CA-125 levels were serially assessed prior to IMT and at follow-up. Lymphocyte subsets were determined on a Beckman Coulter's Epics XL-MCL™ Flow Cytometer and analyzed using the XL SYSTEM II™ software. We evaluated tumor response [CR, partial remission (PR), stable disease (SD), and progressive disease (PD)] according to medical records, imaging studies by Response Evaluation Criteria in Solid Tumors (RECIST) criteria [21], and the Rustin guidelines by measurement of serum CA-125 [22,23]. Data on treatment toxicity were extracted from clinical charts and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v 4.0).

Statistical analysis

In patients with refractory disease, overall survival (OS) was calculated from the date of diagnosis to the date of death. In patients with recurrent disease, survival after recurrence (SAR) was calculated from the date of first recurrence to the date of death. Post-IMT progression-free survival (PFS) and post-IMT survival (PIS) were determined from the date of IMT administration to the date of the subsequent recurrence or death. The disease stabilizing rate was defined by summing up the percentages of CR, PR, and SD lasting for at least 6 months. Descriptive statistics were calculated for all characteristics of the study patients. Survival curves (PFS, OS, SAR, and PIS) were generated using the Kaplan–Meier method. Differences in median values between groups were analyzed with the Mann–Whitney *U* test for comparison of the two independent groups and the Wilcoxon signed ranks test for comparison of the