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Case Report OMICS International

Immunotherapy with Immunomodulatory Agents Prolong Survival of Advanced Ovarian Cancer with Brain Metastatis

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Abstract

The prognosis of patients with metastatic ovarian cancer is poor. Treatment with surgery and chemotherapeutic drugs alone is rarely curative. In the past few years, the development of immunotherapy, targeted therapy, angiogenesis inhibitors, and tyrosine kinase inhibitors has provided better treatment choices for patients with metastatic ovarian cancer.

A 62-year-old woman was diagnosed on October 2008, with advanced ovarian cancer, stage IIIc. She underwent maximal debulking surgery (including abdominal total hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, excision of multiple peritoneal carcinomatosis, bilateral pelvic lymph node dissection, and end-to-end enteroanastomosis) with concurrent intraperitoneal treatment by hyperthermia lavage (5000 ml, 43 cesium degree) with immunomodulatory agent celecoxib (cyclooxygenase-2 inhibitor) to create host immunosurveillance for consolidation therapy. The standard pacitaxol-based chemotherapy totally 6 times were given monthly, combined with immunotherapy. The immunomodulatory agents used were picibail (OK-432), interferon-alpha, celecoxib (cyclooxygenase-2 inhibitor), and aldeleukin (IL-2). We checked her immune risk profiles (IRP) before and after therapy. We found that the operative stress rendered host immunosurveillance switch less immunogenicity [CD4/CD8 ratio less 1] to mimic immunocompromised status.

She had relapse of ovarian cancer with brain metastasis about 28 months later (on Feb 2011). She received surgery, chemo-radiation therapy and immunotherapy (ICRT) for multiple brain metastasis. Later, she had relapse of new lesions over right cerebellum on August 2012 and she received concurrent immunochemoradiotherapy. After whole brain radiotherapy (3000 cGY/ per time) totally 10 times and “add on” standard dose avastin 15 mg/kg and single or combined chemotherapy and dose dense chemotherapy, the metastatic cerebellum tumor had complete remission.

Unfortunately, she was found to have huge right frontal and temporal brain metastasis with extended to 4th ventricle on May 2015. She received manitol and dexan to control her increased intracranial pressure, and followed by avastin (bevacizumab) and immunochemotherapy. Immunomodulatory agents, including picibanil (OK-432), pamidronate, interferon-alpha, celecoxib (cyclooxygenase-2 inhibitor) and chemotherapies (paclitaxol 135 mg/m^2-based chemotherapy per 3 weeks for 6 times) were given. Later, she underwent craniotomy to removal of suspect residual brain metastasis lesion and the pathology showed necrosis brain tissue. The patient achieved a dramatic remission of metastatic brain lesions after “obapac” (OK-432, bevacizumab [avastin], pamidronate, intereferon-alpha, and celecoxib) and chemotherapies.

Our case demonstrates the dramatic promise of immunomodulatory therapy to induce complete remission of a metastatic cancer nodule. This case suggests the potential value of immunotherapy to augment host immunosurveillance to improve survival of metastatic ovarian cancer.

Keywords: Ovarian cancer; Metastatic ovarian cancer; Brain metastasis; Immunotherapy

Introduction

On a global scale, ovarian cancer is a major cancer-related cause of death in women. Early-stage ovarian cancer is curable in most patients

by surgery and/or chemotherapy; but, they cannot achieve 100% durable complete response. The 2-year survival rate of ovarian cancer with brain metastasis is 31.6%. The median survival time in patients with brain metastasis from serous ovarian cancer was 9 months [1]. Thus, we urgently need better therapy for relapse of ovarian cancer, and immunotherapy to augment host immunosurveillance may be the way forward.

Here, we present a case of ovarian cancer IIIc with relapse at brain tissue. Our case demonstrates the dramatic remission of metastatic cancer nodule after immunomodulatory therapy, and the patient has survival for more than 8 years till now. Our case highlights the clinical application of immunotherapy in the case of relapse of advanced ovarian cancer.

Case Report

A 62-year-old woman, G4P3AA1, has progressive abdominal distension with mild intermittent pelvic pain and poor appetite for several months. She came to our hospital on October 2008 and advanced ovarian serous adenocarcinoma, stage IIIc was diagnosed. She underwent maximal debulking surgery (including abdominal total hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, excision of multiple peritoneal carcinomatosis, bilateral pelvic lymph node dissection, and end-to-end enteroanastomosis) with concurrent intraperitoneal treatment by hyperthermia lavage (5000 ml, 43 cesium degree) with immunomodulatory agent celecoxib (cyclooxygenase-2 inhibitor) to create host immunosurveillance for consolidation therapy. In addition to standard chemotherapy (pacitaxol-based chemotherapy totally 6 times were given monthly), combined immunotherapy were given monthly. The immunomodulatory agents (IMA) we used were picibail (OK-432), interferon-alpha, celecoxib (cyclooxygenase-2 inhibitor), and aldeleukin (IL-2). After the HoLANc therapy (hyperthermia, OK-432, lysate, aldeleukin, nutrition and chemotherapy), her condition is stable for more than two years.

She had relapse of ovarian cancer with brain metastasis about 28 months later (on Feburary, 2011). She received surgery, chemo-radiation therapy and immunotherapy (ICRT) for multiple brain metastasis. Later, she had relapse of new lesions over right cerebellum on August 2012 and she received concurrent immunochemoradiotherapy. After whole brain radiotherapy (3000 cGY/ per time) totally 10 times and "add on" standard dose avastin 15 mg/kg and single or combined chemotherapy and dose dense chemotherapy, the metastatic cerebellum tumor had complete remission.

Unfortunately, she was found to have huge right frontal and temporal brain metastasis on May 2015 (Figure 1A). She received manitol and dexan to control her increased intracranial pressure, and followed by chemotherapy (paclitaxol 135 mg/m^2-based chemotherapy per 3 weeks for 6 times) and immunotherapy "obapac" (OK-432, bevacizumab [avastin], pamidronate, intereferon-alpha, and celecoxib. After above therapy, she underwent craniotomy to removal of suspect residual brain metastasis lesion and the pathology showed necrosis brain tissue. It means, the patient achieved a dramatic remission of metastatic brain lesions after above therapy (Figure 1B), and the patient has survival for more than 8 years till now.

Her blood test demonstrated that the circulating leukocytes subsets are WBC 5400, lymphocytes 19.5% (absolute lymphocyte count: ALC 1053/microliter) and transferrin 131 mg/dl (normal range: 200-360 mg/dl) before surgery. After en block operation and immunomodulatory therapy, she restored transferrin to be 197 mg/dl and ALC 1721/microliter on November, 2008. There was no obvious side effects noted during or after the immunomodulatory therapy in our case.

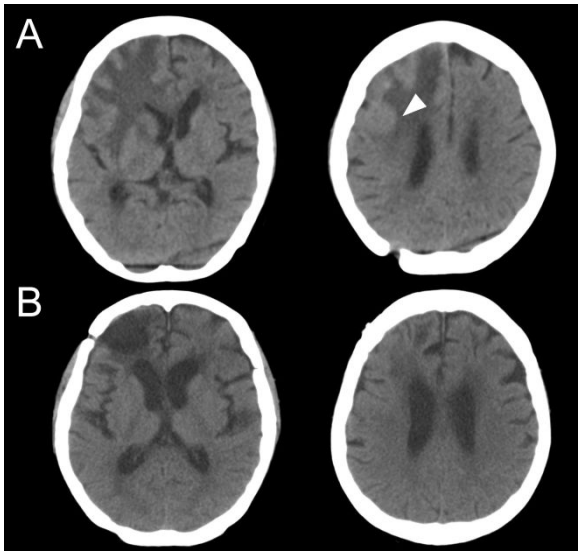

Figure 1: CT image of metastatic brain tumor before treatment (A, arrow head); complete tumor remission and recovery of brain edema in the right frontal lobe after chemotherapy and immunotherapy "obapac" (B).

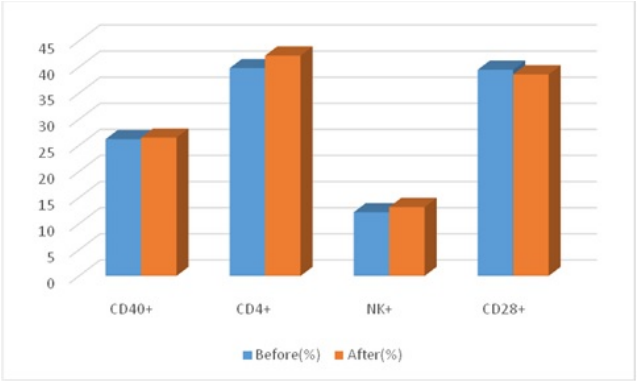

Figure 2: Comparison of IRPs before and after comprehensive staging surgery and immunomodulatory agents (on October, 2008) mimic priming and effector phase to create host immunosurveillance.

We follow the patient's serial immune risk profiles (IRP), including of CD3 (common T cells), CD19 (B cells), NK, and immunoregulatory CD4$^+$, CD25$^+$, CD40$^+$ (antigen presenting cell's marker) and CD28$^+$ immune cells etc (Table 1). We found that the operative stress rendered host immunosurveillance switch less immunogenicity [CD4/CD8 ratio less 1] to mimic immunocompromised status. We also found out reducing original sinks (CD19$^+$, CD8$^+$) in our case after the major surgery procedure. There is an increasing trend in host immunogenicity and efficient anticancer response after priming

surgery and effector phase on October, 2008 (Figure 2). Predominant CD28$^+$ and NK immune cells pathway during memory phase was noted about one month later (on November, 2008) after concurrent chemoimmunotherapy (Figure 3).

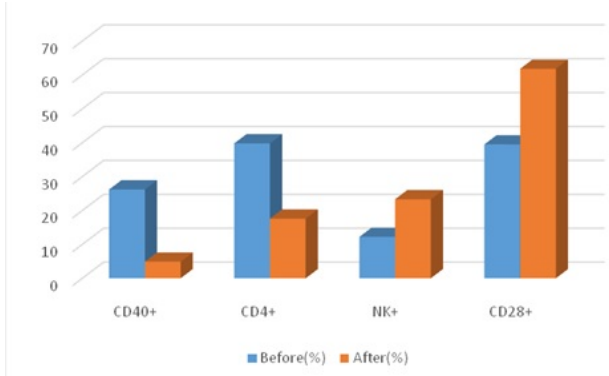

Figure 3: Comparison of IRPs before and after comprehensive staging surgery and immunomodulatory agents (on November, 2008) show predominant CD28$^+$ and NK immune cells pathway during memory phase.

	2008/10/07 Before (%)	2008/10/13 After (%)	2008/11/17 After (%)
T-CD3	60.9	61.2	67.7
B-CD19	25.6	24.1	3.7
CD25	2.1	9.2	1.2
CD4+CD25+	2	8.2	1.1
CD40+	26.2	26.5	4.9
CD19+CD40+	25.3	24	3.6
CD4 T Cell	39.8	42.2	17.6
CD8 T Cell	24.6	23.4	46.1
CD4/CD8	1.6	1.8	0.4
NK-Cell	12.2	13.2	23.3
CD28	39.5	38.6	61.8
CD8+CD28+	5.5	4.6	3.5

Table 1: Immune risk profiles (IRP) comparison before and after en block surgery with immunomodulatory therapy (IMT).

Discussion

To generate potent anti-cancer immunity, antigen-presenting cells, most notably dendritic cells (DCs), must undertake a number of processes. We used adjuvant picibanil (OK-432) to trigger skin naïve DCs to immature DCs to present major histocompatibility complex (MHC) class I and/or Class II, Toll-like receptors or FcR receptor to capture of tumor associated antigens (TAAs) within in situ in vivo immunization. Matured DCs secreted multiple of chemokines and/or cytokines to recruit innate and adaptive immune cells to elicit promising anticancer response [2,3]. Long term CD8$^+$ T cells' efficient anti-cancer response requires CD4$^+$T cells help to maintain host immunosurveillance. Thus, we monitored personal immune risk profiles (IRP) to predict host immunosurveillance (elimination of host's circulating cancer cells) to achieve durable complete response.

In our case, the initial effective cancer therapy depends on immunomodulatory agents followed by maximal debulking surgery and hyperthermia lavage. After the conventional therapies and "add on adjuvants and/or cytokines", activated APCs present multiple cell surface receptors to orchestrate between innate and adaptive immune cells to efficient anticancer response to get durable complete remission [4].

Her circulating leukocytes subsets were WBC 5400 and lymphocytes 19.5% (ALC 1053/microliter) before surgery. After en block operation and chemoimmunotherapy, she restored ALC to be 1721/microliter. The elevation of ALC value represents good outcome via personal immunomodulatory therapy [5].

About her first relapse with multiple brain metastasis, she received surgery, chemo-radiation therapy and immunotherapy (ICRT). The therapy of ICRT trigger stressed protein secreting from inflammatory immune cells and brain tumor cells, and this process mimic to create damaged associated membranous proteins (DAMP). On day 0, radiotherapy and/or chemotherapy procedure, we generated signal "0"; and then on day1, we quickly administered OK-432 subcutaneous injection to augment naïve dendritic cells (DCs) to polarize immature phagocytes' antigen-presenting cells to completely orchestrate fully efficient host immunosurveillance (signal 1 and 2). CD40$^+$ antigen presenting cells elevated after stress operative, such as matured DCs (CD83$^+$ immune cells) can secrete multiple chemokines and/or cytokines to recruit innate and adaptive immune cells to elicit promising anticancer response, and long term CD8$^+$ T cells' efficient anti-cancer response requires CD4$^+$ T cells help to maintain host immunosurveillance [6].

About the treatment for her huge frontal and temporal area brain metastasis, she received continuously bevacizumab (avastin) one vial 100 mg-based immunochemotherapy (ICT) per monthly. Under immunomodulatory "Obapac" therapy, it generate complete remission of huge brain metastasis tumor with pathologic necrosis cells.

About the IRP in our patient, we evaluated at least three components. Stimulatory molecules included CD28 (naive or juvenile marker), CD40$^+$, CD40L (CD154), NK etc. Inhibitory molecules included B cells (CD19), CD25, NKT etc. Finally, immunosuppressive and/or immunoregulatory molecules included CD4$^+$ CD25$^+$T cells, CD11b$^+$ (myeloid derived suppressive cells) etc. The purpose of monitoring the patient's IRP is to evaluate host immunosurveillance (i.e., elimination of host's circulating cancer cells) to achieve a durable complete response. The markers shown in Table 1 included CD3 (T-cell), CD19 (B-cell), CD25, CD4 (helper T-cell), CD8 (T-cell), NK, CD40 (immature Dendritic cell), and CD28 (co-stimulatory marker) before and after the enblock surgery, intraperitoneal hyperthermia lavage and immunochemotherapy. The IRP revealed CD4/CD8 ratio to normalize (from 1.6 to 1.8), elevated CD4$^+$ T cells from 39.8 to 42.2%, CD40$^+$ antigen presenting immune cells enhance 1.01 fold (from 26.2 to 26.5%) after major surgery procedure. We found out reducing original sinks (CD19$^+$, CD8$^+$) in our case after the major surgery procedure. We also find out declined B cell from 25.6 to 24.1%. This result showed an increasing trend in host immunogenicity and efficient anticancer response after priming surgery and effector phase (Figure

2). Predominant $CD28^+$ and NK immune cells pathway during memory phase was noted about one month later after concurrent chemoimmunotherapy (Figure 3). Similar findings had been reported in previous study, patients who received surgical procedures' stress will facilitate immune signal 2 [7].

In conclusion, efficient immunity depends on signals delivered through the antigen-specific T-cell receptor (signal 1), costimulatory receptors on T cells (signal 2), and immunomodulatory agents and/or cytokines (signal 3) to achieve a long term durable anticancer response. Our case highlights the clinical significance of immunotherapy in case of relapse of advanced ovarian cancer.

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- This study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital, Taoyuan, Taiwan (100- 3902A3).

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