ORIGINAL ARTICLES

Malignant mixed mesodermal tumor of the ovary treated with a cisplatin-irinotecan combination: case report

P. Azevedo, C. F. Verschraegen, J. J. Kavanagh, A. P. Kudelka, R. S. Freedman, K. Lu, M. T. Deavers

Multidisciplinary Gynecologic Cancer Center, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas (USA)

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Introduction

Sarcomas of the female reproductive tract may be classified into two different pathologic categories. Pure sarcomas, containing only a malignant mesenchymal component, include pure homologous, pure heterologous, or pure mixed sarcomas. Malignant mixed Mullerian tumors (MMMT), containing a malignant mesenchymal component admixed with an epithelial component, include homologous or heterologous elements [1]. The latter refers to mesenchymal elements not normally present in the female genital tract (i.e. cartilage, bone fat, striated muscle [2]. The most common forms of sarcomas are leiomyosarcoma, endometrial stromal sarcoma, malignant mixed mullerian tumors, adenosarcoma, and others [3]. These sarcomas have different biological behaviors, and clinically, should be studied separately. Among these, MMMT is by definition the only cancer consisting of both sarcomatous and carcinomatous components [4]. It arises in decreasing frequency in the uterine corpus, uterine cervix, vagina, ovaries, uterine tubes, and peritoneal lining [5].

MMMTs comprise less than 2% of all ovarian malignancies [2]. They tend to be aggressive, with a median 5-year survival of approximately 31% [6]. The majority of studies show no survival advantage for those who have had pelvic radiation [7-10], and the tumor tends to recur in 56% of the cases, even at early stages [11]. This suggests the need for effective systemic therapy. Of the many single agents that have been tried, cisplatin and ifosfamide appear to be the most efficacious, with a response rate around 18% for each drug [12, 13]. Cisplatin showed similar activity as first or second-line treatment [13, 14]. More recently, combination chemotherapy options have been tried and, again, those based on cisplatin appear to be the most promising, with a 30 to 40% response rate [15, 16]. However responses are of short duration, and the patients often die following recurrence [17]. We report a case of a patient with recurrent ovarian MMMT that achieved a prolonged surgically confirmed complete response after second-line treatment with a cisplatin and irinotecan combination.

Case Report

A 63-year-old white female presented to her primary care physician with urinary incontinence, fever and fatigue. The past medical history was remarkable for a hysterectomy at age 38 for cervical dysplasia, birth control pill intake, and cigarette smoking for 45 years. Her mother had ovarian cancer and her father head and neck cancer. An abdominal ultrasound showed a pelvic mass, and the patient underwent exploratory laparotomy with bilateral salpingo-oophorectomy, omentectomy and optimal tumor reductive surgery. She was found to have MMMT in both the ovaries and the omentum. Pathologically, the majority of the tumor consisted of undifferentiated carcinoma with foci of high-grade serous carcinoma. The sarcomatous component was predominantly high-grade unclassified pleomorphic sarcoma with foci of chondrosarcoma and a low-grade spindle cell component. The patient started a carboplatin and paclitaxel combination chemotherapy for a total of six courses [18]. Serial measurements of CA125 showed a decrease to normal range. She was then put on Premarin 0.625 mg every day orally. Five months after the end of the carboplatin and paclitaxel treatment, the CA-125 level rose to 34 IU/ml, then to greater than 500 IU/ml, and a recurrence was diagnosed by CT-scan. A diagnostic laparoscopy showed extensive recurrence in the omentum and the anterior abdominal wall, as well as extensive intra-abdominal adhesions. The pathology examination revealed recurrent metastatic adenocarcinoma consistent with ovarian primary. Considering the adhesions and the extent of disease, a decision was made to treat her with cytoreductive chemotherapy. A combination of cisplatin 50mg/m2 on day 1 and irinotecan 50 mg/m2 on days 1, 8, and 15 repeated every four weeks was administered. After 2 cycles she had a marked clinical improvement and the CA-125 dropped from 646 to 88. After 5 cycles the abdominal CT scan had normalized, and the CA-125 was 13. Two more cycles of consolidation were given. During the last one she was hospitalized for an acute episode of pancreatitis due to gallstones. Abdominal exploration and multiple biopsies were conducted during an elective cholecystectomy, performed one month later. All the biopsies were found to be negative. The patient has remained in complete remission for six months after this surgical intervention.

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Discussion

MMMT affects mainly postmenopausal women. The median age at diagnosis is 60 to 66 years [2, 6, 19]. The most common symptoms at presentation are lower abdominal pain, abdominal enlargement, and pelvic heaviness [2, 17]. For disease originating in the uterus, 60% of patients are diagnosed at stage I, 20% at stage II, and 10% at stages III and IV [11]. For disease originating in the ovary, most patients are diagnosed at stage III and above [17]. The etiology and risk factors are not well established, and need to be clarified. However exposure to hormones has been incriminated in the etiology of uterine sarcomas [20, 21]. Several prognostic factors have been reported in the literature, such as tumor size, extent of disease, lymph node metastasis and grade of the sarcomatous component of the tumor [11]. The homologous cell type is believed by some authors to be of better prognosis. A GOG study with 301 patients showed a longer progression-free index at three years for the homologous type (55% versus 43% for the heterologous group), and a lower recurrence rate (44% versus 63%) [11]. Others saw no mortality difference between cell types [22]. The primary site in the genital tract has not been considered to be of importance regarding prognosis or treatment response [1]. The staging normally follows the FIGO pattern for the site in which the tumor arises.

Due to the low incidence of this tumor, large prospective studies are very difficult to perform. Thus, little is established about the management of this malignancy. Cytoreductive surgery remains the cornerstone of the treatment [1]. Indeed, it has been suggested that the absence of residual disease after surgery correlates with an improved survival [16]. There is no consensus about lymphadenectomy. This procedure appears to be of staging importance, but does not improve survival or prevent recurrence. Radiation therapy is also controversial. Although most authors believe radiotherapy does not impact survival, the majority agrees that it could confer better local control [9, 10]. Twenty percent of patients have lymph node metastases at diagnosis [10, 11]. Seventy-five to 85% of recurrences occur outside of the pelvis [8, 15]. This suggests the need for systemic therapy. Many agents have been tried. Single-agent therapy with etoposide [19], piperazinedione [23], mitoxantrone [24], or doxorubicin [25] have been disappointing. Platinum based combination chemotherapies appear to be the most promising [15, 26]. In one study, the combination of cisplatin, doxorubicin and etoposide was tested as first line after debulking surgery in 42 patients at various stages of the disease [7]. Outcomes of therapy were evaluated with recurrence and overall survival. Responses (2 complete and 2 partial) were observed in four patients with evaluable disease. In patients with MMMT arising from the ovary, the response rate to cisplatin-based combination varies from 35 to 80% of patients [1]. But despite improvement in the rate of response, the median survival does not exceed two years (9 to 18 months).

The rationale for combining cisplatin and a topoisomerase-I inhibitor derives from preclinical studies showing synergism. SN-38 (the active metabolite of irinotecan) shows synergic activity with cisplatin, fluoracil and etoposide in vitro [27]. The topoisomerase-I inhibitors may interfere with the repair of the DNA damage caused by cisplatin [28]. In recent clinical studies performed in gastrointestinal cancers, and cervical and ovarian cancers, high response rates have been achieved [29, 30]. Responses after combination treatments including a topoisomerase-I inhibitor are observed in 40 to 70% of patients.

Because the patient we describe had a peritoneal recurrence consisting mainly of the carcinoma component, we decided to try the potentially synergistic platinum-based combination with irinotecan. Cisplatin was chosen over carboplatin because of the potential for myelotoxicity and thrombocytopenia with the latter drug. Based on preclinical studies of schedule of topoisomerase-I inhibitor administration, continued exposure to these agents are important to maintain response [31]. Therefore, we chose a schedule where dose reduction or dose skipping would be minimized. This patient had a 6-month complete pathologic remission after second-line treatment with cisplatin and irinotecan. She tolerated the treatment well with fatigue as the main side-effect.

Conclusions

Although responses to chemotherapy from MMMT are not rare, the duration of these responses is short, and the disease tends to recur quickly. Better regimens are needed as first and second-line therapy. In this case, cisplatin and irinotecan combination administered as second line provided a longer disease-free interval than the first-line therapy of carboplatin and paclitaxel. Therefore, the combination of platinum and irinotecan deserves to be further evaluated in the treatment of this malignancy.

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Address reprint requests to:
C. F. VERSCHRAEGEN, M.D.
The University of Texas
M.D. Anderson Cancer Center
1515 Holcombe Boulevard, Box 401
Houston, Texas 77030 (USA)