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Isolated Leptomeningeal Metastasis from Ovarian Carcinoma: an Unusual Event

J.P. Delord, K. Fizazi, M. El Hajj, P. Pautier and C. Lhommé

Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif, France

OVARIAN CARCINOMA is the third highest cancer-related cause of mortality in women. A review of 255 patients with epithelial ovarian carcinoma revealed that metastasis develops in 40% of patients (50% if autopsy is performed) at some time during the natural history of their disease [1]. Distant metastasis seldom occurs in the absence of intra-abdominal disease. The liver, lung and distant lymph nodes are the most common sites of metastatic disease, along with malignant pleural effusion. Bone metastasis and central nervous system (CNS) metastasis are rare and occur late in the evolution of the disease. Less than 2% of patients develop clinical evidence of cerebral disease. Such lesions usually exhibit contrast uptake on computed tomography (CT) scans and are located in the cerebral hemispheres [2, 3]. Leptomeningeal metastasis, presenting as a single lesion of the CNS and negative on magnetic resonance imaging (MRI) or CT scan, is exceptional and more frequently reported in breast cancer and lung cancer [4]. This situation has recently been described in only one of 23 patients with CNS metastasis from ovarian carcinoma [5]. 2 other cases have been mentioned in older studies [6, 7]. Here we present a case report from our institute. A 57-year-old woman was diagnosed as suffering from a FIGO stage III B adenocarcinoma of the ovary in November 1987. She underwent a hysterectomy and bilateral salpingo-oophorectomy. Postoperatively, she received six courses of chemotherapy combining carboplatin and cyclophosphamide. A second laparotomy was performed and no microscopic residual disease was found in the omentum. The patient received abdominopelvic irradiation as consolidation. In September 1991, generalised peritoneal carcinomatosis was found. Salvage chemotherapy combining cisplatin and doxorubicin was administered and a clinical and biological complete remission was obtained, but with grade II peripheral neuropathy.

Between November 1996 and March 1997, she received seven cycles of paclitaxel, due to isolated elevation of serum Ca 125. The patient was well until April 1997, when she began to complain of increasing paresthesia and deafness and Ca 125 increased again. Examination of the head and neck and CT scan led to the diagnosis of maxillary infection and otitis which were effectively treated with antibiotics. Only peripheral neuropathy was found at neurological examination. No parenchymal lesion was detected on the brain CT scan. Consequently, chemotherapy-related toxicity was suspected.

Blurred vision confined to the left eye, dizziness and unsteady gait appeared 4 weeks later. The patient was finally hospitalised in the emergency unit because of severe headaches and radicular pain, without nuchal rigidity. An MRI was performed, but no evidence of brain or leptomeningeal metastasis was found. The diagnosis of meningeal carcinomatosis was finally confirmed when malignant cells were detected in the cerebrospinal fluid. Intrathecal injections of methotrexate were initiated, but the patient rapidly presented mental confusion, nuchal rigidity and deterioration of her general condition. She finally died 2 days later in a context of intravascular coagulation. At the time of death there was no evidence of recurrent peritoneal carcinomatosis. No sign of infection nor secondary cancer was found at complete clinical examination. An autopsy was not performed.

CNS metastasis from ovarian cancer is uncommon, while leptomeningeal metastases are even more rare. Advances in surgery and chemotherapy have led to higher remission rates and a trend towards a longer median survival. With effective combination chemotherapy with new drugs and longer survival, hitherto occult CNS metastases are probably becoming apparent. The CNS may be a 'pharmacological sanctuary', which is not always readily accessible to drugs, even when high intravenous doses are administered. However, adequate concentrations of cisplatin have been found in the CNS and a complete remission of cerebral metastasis from ovarian carcinoma has been reported after carboplatin [8]. To date, only minute traces of paclitaxel are reported have penetrated the brain and cerebrospinal fluid [9]. This could be the reason why leptomeningeal metastases are detected during paclitaxel single-agent therapy [10], although the disease appears to be controlled elsewhere.

Correspondence to J.P. Delord.
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Phase II Trial of MINE as a Front-line Therapeutic Modality in Intermediate- and High-grade Non-Hodgkin's Lymphomas

I. Çelik, A. Kars, N. Güler, I. Barışta, G. Tekuzman, Ö. Özyılkan, M. Hayran and D. Fırat

Department of Medical Oncology, Hacettepe University Institute of Oncology, 06100 Sihhiye, Ankara, Turkey

NON-ODGKIN´S lymphomas (NHLs) are a heterogenous group of disease both in natural history and in their response to therapy. Patients with low-grade NHLs have usually an indolent but incurable disease in whom currently available therapeutic methods could offer only palliation. On the contrary, the vast majority of intermediate-grade and almost all high-grade NHLs exhibit an aggressive course, but also have a potential for cure when treated with combination chemotherapy. Nevertheless, the response of intermediate- and high-grade NHLs to conventional anthracycline combinations is still unsatisfactory and almost 50% of patients either do not achieve complete remission (CR) or eventually relapse after CR [1].

Identification of new drugs or combinations and incorporation of successful salvage regimens to the front-line treatments are the novel alternatives for the convenient management of aggressive NHLs [2, 3]. As the data of our previous study precluded no superiority of several first-line anthracycline combinations to each other by means of response and survival [4], we instituted a phase II trial of MINE (mesna, ifosfamide, mitoxantrone and etoposide) chemotherapy in previously untreated patients with intermediate- and high-grade NHLs to assess the response rate and the toxicity profile of this regimen.

Between 1990 and 1994, 32 patients with a mean age of 47.3 years (range 19–65) and a male/female ratio of 18/14 were prospectively recruited. There were 15 intermediate- and 17 high-grade NHLs according to the Working Formulation (excluding lymphoblastic lymphoma and adult T-cell leukaemia/lymphoma). After initial evaluation and staging procedures, patients received MINE chemotherapy consisting of ifosfamide 3 g/m^2 with mesna 3 g/m^2, i.v. (intravenous) 8 h infusion, on day 1; mitoxantrone 12 mg/m^2, i.v. 24 h infusion on day 1 and etoposide 100 mg/m^2, i.v. 1 h infusion, on day 1, to be repeated every 4th week. Patients achieving CR or partial remission (PR) after three courses received three more cycles to a total number of six.

The overall response rate was 65.7% (21/32 pts) (46.9% CR(15/32)+ 18.8% PR (6/32)) after a total of 148 and a median of 6 chemotherapy cycles. Median time to progression (TTP) was calculated to be 21.4 months (95% CI of 9.3–33.9) with a relapse rate of 62% after a median follow-up of 30 months (range 12–40). 4 unrelapsed patients (3 high- and 1 intermediate-grade NHLs) were long-term responders, after 30, 32, 36, and 40 months, with a possibility of cure. Univariate analysis of pretreatment factors disclosed shorter ($P < 0.05$) TTP in the presence of advanced stage, bulky disease and in patients with poor performance status (> 2, ECOG scale). Multivariate analysis revealed TTP to be significantly influenced by the presence of bulky disease and older age; i.e. patients with bulky disease had an 8.1-fold increased relapse risk compared with those without and increased age added a relapse risk of 1.07 per year.

The MINE regimen was generally well tolerated and no toxic death was encountered during or after chemotherapy courses. WHO grade 2–3 alopecia (92%), grade 2 nausea and/or vomiting (90%), grade 2–3 myelosuppression (74%) and grade 2–3 infectious complications (29%) were the most common toxicities. No hepatic, renal (including haemorrhagic cystitis) or cardiac toxicity was documented.

Mitoxantrone, a dihydroxyanthracenedione derivative, has been demonstrated to be an effective and better tolerated alternative in the salvage treatment of NHLs: mitoxantrone monotherapy providing a response rate of 40% [5], the combination of ifosfamide and mitoxantrone with a response rate up to 50% [3] and further addition of etoposide to the regimen yielding almost 70% response rate in previously treated patients with NHL [6]. Even though the data favours utilisation of mitoxantrone combinations as a first-line polychemotherapy for NHL, to date the results of this sort of trial have been lacking [2].

In this phase II trial, the characteristics of response regarding the pretreatment prognostic factors and the toxicity profile of front-line MINE regimen in patients with intermediate- and high-grade NHL have been documented. Despite the acceptable overall response rate obtained, certain limitations, such as the presence of a few long-term disease-free survivors and higher cost and toxicity, make a first-line MINE regimen unlikely to be an alternative to the conventional chemotherapy protocols. Nevertheless, future comparative phase III studies are warranted to draw more definitive conclusions.

Correspondence to I. Çelik.
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