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Case Report

A Case Report of Uncommon Efficacy and Favorable Safety Profile of Gemcitabine Rechallenge in Metastatic Breast Cancer

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Abstract

Currently, many cytotoxic and targeted therapies can be used to treat Metastatic Breast Cancer (MBC), but despite their effectiveness, they are often associated with significant toxicities and de novo or acquired resistance. In clinical practice a small subset of patients show a strong and prolonged response to less toxic and active regimens, usually left as late treatments, as gemcitabine.

We describe the case of a woman with MBC who obtained very limited benefit from the most commonly used drugs, but reached the complete remission of disease after the treatment with gemcitabine, even when rechallenged several times. The further addition of trastuzumab had significantly improved the efficacy of gemcitabine, with acceptable toxicity. Thanks to gemcitabine rechallenge, the patient survived for almost 13 years with MBC, maintaining a good quality of life.

Gemcitabine rechallenge should be considered when patient previously obtained complete remission of disease with this drug. Predictive biomarkers for the detection of patients that would benefit from a well-tolerated treatment as gemcitabine, eventually avoiding or delaying more toxic regimens, are urgently needed.

Keywords: Metastatic breast cancer; Gemcitabine; Complete remission

Abbreviations

CI: Confidence Interval; CMF: Cyclophospamide Methotrexate 5-Fluorouracyl; CR: Complete Response; ECOG: Eastern Cooperative Oncology Group; G2: Grade 2; Gy: Gray; HRs: Hormone Receptors; IHC: Immuno Histo Chemistry; MBC: Metastatic Breast Cancer; OS: Overall Survival; PD: Progressive Disease; PR: Partial Response; PTS: Patients; QoL: Quality of Life; RR: Response Rate; SD: Stable Disease; T-DM1: ado-Trastuzumab-emtansine; TTP: Time To Progression

Introduction

Breast cancer affects approximately 12% of women worldwide and results in 14% of all cancer-related deaths [1]. Despite the diffusion of screening programs, about 6% of women still have metastatic disease at the onset presentation [2,3]. Median Overall Survival (OS) of patients with Metastatic Breast Cancer (MBC) is extremely variable (8 months to 4 years) [4,5]. In the last decades, with the advent of new cytotoxic drugs and targeted therapies, a significant increase in OS of MBC patients has been achieved. Nevertheless, in the majority of cases, after an initial response to treatment, the development of highly aggressive and drug-resistant disease is commonly observed [6]. For these reasons, the current goals are not only the prolongation of OS, but also the improvement of the Quality of Life (QoL) through disease control and drug-related toxicities management. Gemcitabine (2',2'-difluorodeoxycytidine) is a nucleoside analog that makes its antiproliferative activity through two active metabolites, gemcitabine di- and triphosphate [7]. The safety profile is good with a limited, mainly hematological, toxicity. This drug has been approved not only for the treatment of MBC but also for pancreatic [8], lung [9], bladder [10] and ovarian tumors [11]. Even if gemcitabine has been shown to be effective in combination with paclitaxel for the first-line treatment of MBC [12], its use as single agent in pre-treated patients has given only a small benefit in several reports [13,14]. Here we report the case of a MBC patient that, after several failing attempts with drugs commonly more effective than gemcitabine, achieved the complete remission of disease with this antimetabolite in more than one treatment-line. The overall benefit from the drug lasted more than 10 years. This case report highlights the existence of a small percentage of MBC patients that could obtain a terrific benefit from a low toxic and often underestimated drug for this pathology, in urgent need for new predictive biomarkers.

Case Presentation

We describe the case of a 52-year old caucasian woman, in good clinical condition (ECOG performance status: 0), affected by essential hypertension, chronic hepatitis C infection and mild depressive syndrome. In January 1999, she underwent left upper quadrantectomy and ipsilateral axillary lymphadenectomy. The pathology report showed a bifocal invasive ductal carcinoma (stage pT2N3M0); by immunohistochemistry, neoplastic cells stained positive for Her2 (IHC: 3+) and negative for Hormone Receptors (HRs). Chemotherapy (4 cycles of doxorubicin plus paclitaxel q21, followed by CMF 1-8q28, for 4 cycles) and radiotherapy (50 Gy) were performed with adjuvant intent. Three years later, on June 2002,

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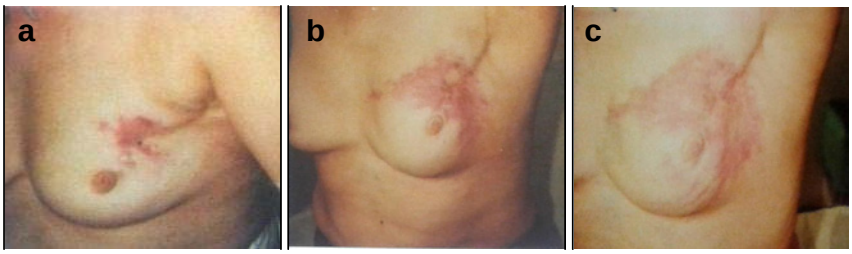

Figure 1: Cutaneous metastasis from breast cancer. **a)** First relapse of disease on the left breast, near the surgical scar. **b)** Cutaneous progressive disease after the 1st-line treatment with water-soluble semi-synthetic analogue of epothilone B. **c)** Partial response of disease after the 2nd-line treatment with capecitabine.

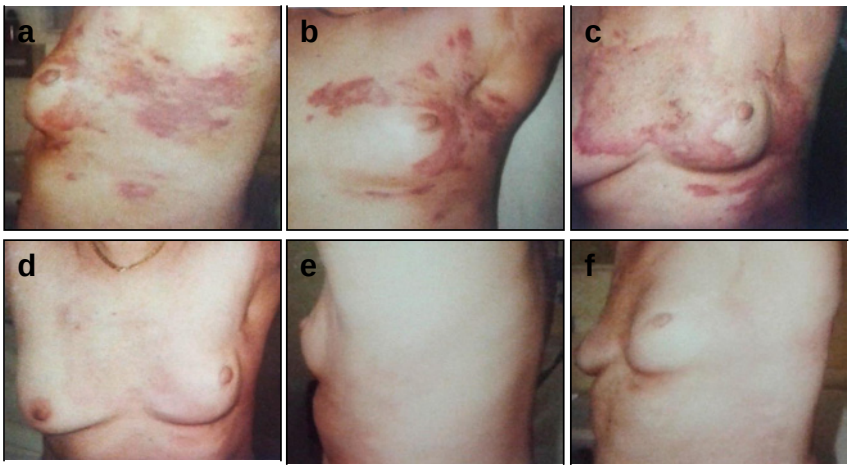

Figure 2: Cutaneous metastasis from breast cancer before and after the treatment with gemcitabine. **a-b)** Cutaneous progressive disease after the 2nd-line treatment with capecitabine. **c)** Cutaneous progressive disease after the 4th-line treatment with docetaxel. **d-f)** Cutaneous complete remission of disease after the 5th-line treatment with gemcitabine.

metastatic cutaneous nodules appeared near surgical scar (Figure 1a): receptor status was consistent with the primary lesion (HRs, Her2+). Patient was enrolled in a phase I clinical trial with an analogue of epothilone B: after the second cycle of treatment, patient experienced cutaneous Progressive Disease (PD) (Figure 1b). From September 2002, patient received capecitabine, vinorelbine plus trastuzumab, and docetaxel, with poor and short-lasting results (Figure 1c, Figure 2a, Figure 2b and Figure 2c). In January 2004, the patient received gemcitabine for the first time (800mg/m2, day 1-8q21) and after only 4 cycles she achieved a Complete Response (CR) (Figure 2d and Figure 2f). In August 2004, we stopped the treatment because of asymptomatic thrombocytopenia and persistent CR. Two months later a right axillary pathologic lymphnode appeared and patient underwent node dissection (pathology report: HRs, Her2+). In November 2004, new cutaneous nodules appeared and we decided to restart gemcitabine. The rechallenge was extremely effective, bringing to cutaneous CR after only two cycles. In April 2005, mild persistent thrombocytopenia imposed a stop: patient was in CR so we started a strict follow-up. The disease did not relapse for two years until January 2007, when cutaneous nodules appeared. Using gemcitabine for other two rechallenges, cutaneous CR was obtained, with no significant toxicity, until August 2009. After a short attempt with capecitabine plus lapatinib (PD after 4 months), trastuzumab was reintroduced. No significant benefit by the combinations of the monoclonal antibody with both systemic drugs (vinorelbine, topic 5-fluoruracil, lapatinib) and chest wall radiotherapy (5 Gy) was achieved, resulting in extended cutaneous localization at the anterior chest wall. The 5th rechallenge of gemcitabine, at half of the previous dose in consideration of a persistent mild thrombocytopenia, led to an unexpected CR. From December 2010 chemotherapy was administeredin combination with Trastuzumab, and then was stopped because of persistent grade 2 thrombocytopeniain September 2011. Trastuzumab was continued, having no side effects and maintaining the CR until February 2013, when a left supra-clavicular adenopathy appeared (at the biopsy, HRs and Her2+). The introduction of gemcitabine for the 6th time in the therapeutic strategy, without trastuzumab interruptions, brought to the umpteenth CR. In July 2014, the patient developed lung metastases and nodal relapse (left supra-clavicular and mediastinum). The combination of gemcitabine (7th rechallenge) with trastuzumab obtained Partial Response (PR) of lung metastases and Stable Disease (SD) of node lesions after 5 cycles of treatment. From 2002, year of metastatic disease diagnosis, to 2014, patient had no significant toxicities affecting her lifestyle or interfering with her daily-life activities (Figure 3). In more than 5 years of continuative trastuzumab, cardiac function has always been in normal range. On January 2015, heart failure with left ventricular dysfunction occurred (ejection fraction 45%). Trastuzumab was interrupted, medical therapy was performed and patient recovered in few days. Adotrastuzumab-emtansine (T-DM1) was started due to a lung and left supra-clavicular node progression, without any

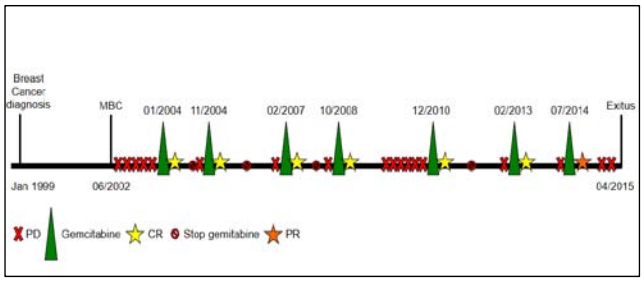

Figure 3: Timeline of patient's treatments and responses.

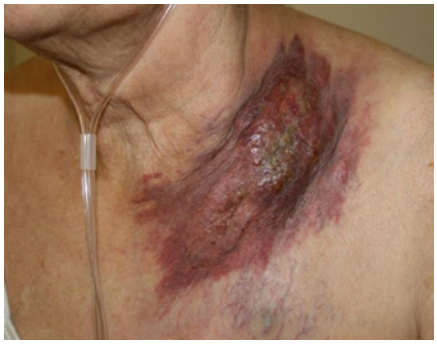

Figure 4: Left supra-clavicular node progression of disease after trastuzumab.

further clinical benefit (Figure 4). Finally, palliative supportive care was activated, until the death of the patient on April 2015.

Conclusion

Despite the advent of targeted therapies, MBC is still considered an incurable disease for the majority of patients. The current milestone for the decision-making process is the biomolecular classification of the disease but, unfortunately, it does not always correspond to drugs sensitivity. Furthermore, patients have to deal with *de novo* or acquired resistance, leading to the shift from one regimen to another, with considerably impact on the QoL. In absence of personalized predictive factors, oncologists need to choose the chemotherapeutic regimen which has the highest likelihood to benefit the patient, but that is often burden with side effects and cumulative toxicities. Here we report the case of a patient that obtained an extraordinary benefit from gemcitabine, a drug that is considered as a last attempt for MBC patients in most of the cases. Moreover, efficacy is accompanied by a good safety profile: the only toxicities were mild thrombocytopenia and fatigue, not impacting with patient's daily activity. This case shows the existence of a subgroup of patients highly sensitive to gemcitabine. It is now crucial to identify this subpopulation, using predictive biomarkers of response, in order to provide a valid and less toxic therapeutic option.

After the advent of gemcitabine in clinical practice [15], several clinical trials have evaluated its role [16] in monotherapy as salvage chemotherapy in heavily pretreated MBC proving that it is effective and safe [13-15,17-24] (Table 1). Better results are achieved if the single agent is combined with cisplatin [25], docetaxel [26], paclitaxel, or vinorelbine [27], taxane plus doxorubicin [28] or taxane plus trastuzumab [29].

Table 1: Published clinical trials evaluating gemcitabine monotherapy in MBC patients.

Reference	No. of Prior Treatments	Median TTP (Months)	ORR%	Median Survival Time(Months)
Carmichael, et al. 1995 [15]	Adjuvant 7 pts 1st-line 14 pts 2nd-line 19 pts Anthracyclines 17 pts	2.1 Median response duration: 13.5 (range 6-43+)	25	11.5
Possinger, et al. 1999 [19]	Adjuvant 10 pts 1st-line 42 pts	3.8	14.3	15.2
Schmid, et al. 1999 [21]	Adjuvant 10 pts 1st-line 4 pts 2nd-line 5 pts ≥ 3rd line 11 pts Anthracyclines 15 pts	6.3 (range 2-23)	25 ≥ 3rd line 18	NA
Brodowicz, et al. 2000 [18]	2nd-line 9 pts 3rd-line 16 pts Anthracyclines 25 pts Taxanes 6 pts	3.6 2nd-line: 5.1 3rd-line: 3.5	16 2nd-line: 22 3rd-line: 13	8.1 (range 2-30.8) 2nd-line: 12.6 3rd-line: 7.5
Smorenburg, et al. 2001 [17]	Adjuvant 11pts 2nd-line 3 pts ≥ 3rd line 20 pts	1.9 (range 1.0-4.4)	0	7.9
Spielmann, et al. 2001 [23]	Antracyclines 47 pts	8.1 (range 2.5-27.4)	29	18.6 (range 0.3-42.0)
Blackstein, et al. 2002 [20]	Adjuvant 19 pts 1st-line 39 pts	5.1 (range 3.5-8.8)	37.1	21.1 (range 11.0-26.9)
Modi, et al. 2005 [14]	2nd-line 4 pts 3rd-line 9 pts 4th-line 7 pts 5th-line 2 pts	NA	17	9.5 (range 6.5-39.6)
Rha, et al. 2005 [13]	3rd-line 26 pts 4th-line 12 pts	4.5 (range 3-5)	20	11 (range 4-18) 3rd-line 12 4th-line 7
Suzuki, et al. 2009 [24]	Antracyclines and taxanes 62 pts	92 days (range 29-651 days)	8.1	17.8

TTP: Time To Progression; ORR: Overall Response Rate; pts: patients; NA: Not Available

Gemcitabine monotherapy reached Response Rates (RR) of up to 37% in the first-line, 26% in the second-line, and 18% in the third-line setting; median Time To Progression (TTP) was within 2 and 8 months, while median overall survival was 8 to 21 months.

In our context, considering the HER-2 positive status of the patient, firstly we added trastuzumab to gemcitabine [30-32], and then we used trastuzumab beyond progression [33], with good results. Concerning to the safety, a single episode of heart failure occurred in our case, which readily regressed stopping trastuzumab and using medical therapy.

There is a vast arsenal of therapies to treat patients in the metastatic setting; in order to select the appropriate therapeutic strategy, the specific characteristics of the illness as well as the personal wishes of patient should be respected. In the era of targeted drugs, in which therapies are more and more personalized, it is crucial to identify predictive factors that can help us to better select patients who can benefit from each treatment in a wide heterogeneous disease like breast cancer. Being the majority of MBC only slightly sensitive to gemcitabine, more studies are needed to identify predictive biomarkers of sensitivity. These clinical instruments would help physicians in the selection of patients that are expected to obtain a strong and prolonged benefit from gemcitabine, eventually avoiding more toxic chemotherapeutic regimens.

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