

Off-label Use of Oxaliplatin in Patients with Metastatic Breast Cancer*

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Abstract. *Background: Oxaliplatin is an anticancer agent only approved for treatment of colorectal cancer, but that has shown some activity in metastatic breast cancer in phase II studies. Herein, we examine the off-label use of oxaliplatin in unselected patients with metastatic breast cancer. Patients and Methods: A retrospective review was performed of all patients with metastatic breast cancer treated with oxaliplatin at our hospital between February 2003 and November 2009. Data concerning patterns of use, safety and activity were collected from patient charts. Results: The cohort comprised 30 female patients with a median age of 49 (range, 34-68 years) and a median of two involved organs (range, 1-4). All patients had been pretreated for metastatic breast cancer (median number of previous lines: 3; range:1-6). Oxaliplatin was only given in association either with fluorouracil and folinic acid (n=23) or with gemcitabine (n=7). The most commonly used dose was 100 mg/m² given every other week or every 3 weeks. As of December 15, 2009, the median duration of treatment was 4 (range, 0.75-11) months. Most of the discontinuations occurred due to disease progression (n=11) and adverse effects or worsening condition (n=8). Twelve (40%) patients presented side-effects related to oxaliplatin use including hematotoxicity (n=8), gastrointestinal disorders (n=4) and neuropathies (n=2). Among patients evaluable for antitumoral activity (n=15), one patient achieved a complete response and one patient demonstrated a partial response. Most of the patients (57%) continued to be treated by chemotherapy after oxaliplatin. Median overall survival for the evaluable patients was 10 (range, 1-51) months. Conclusion: In our population of heavily pretreated women with metastatic breast cancer, off-label use of oxaliplatin was of little worth.*

This off-label treatment was not the last therapeutic option for most of these patients.

Off-label use (*i.e.* outside the official labeling) of anticancer agents may constitute a reasonable and sometimes final therapeutic alternative for patients with refractory tumors or who are intolerant to approved drugs or non-eligible for investigational agents. Thus, off-label use is mainly observed for pretreated patients with advanced disease (1). The real benefits of off-label drug use in oncology are poorly documented (1). Off-label use is generally based on published scientific data and has to provide a significant activity with a good quality of life. Previously, we found that oxaliplatin in pretreated metastatic breast cancer was one of the most frequent situations of off-label prescribing in a general population of ambulatory cancer patients on chemotherapy (2, 3). Eighteen percent of off-label use was observed for patients with breast cancer (including early stage and metastatic disease), while off-label prescribing represented 3.7% of the chemotherapies for this type of tumor (2). Oxaliplatin was the most frequently used agent (77%) in the off-label treatment of breast cancer (2). Off-label use of oxaliplatin is not really surprising because it is a broad-spectrum agent (by analogy to its congeners cisplatin and carboplatin) that, paradoxically, has only been approved (in association) for treatment of colorectal cancer. Oxaliplatin has shown some activity in pretreated metastatic breast cancer. Phase II or pilot studies including patients with pretreated metastatic breast cancer have reported overall response rates (ORR) of 21% for oxaliplatin given alone and ranging from 7.5 to 35% when combined with other anticancer agents (4-13). Assessment of off-label use of oxaliplatin in routine clinical practice has not been reported. Herein, we examine the off-label use of oxaliplatin in unselected patients with metastatic breast cancer.

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Patients and Methods

We performed a retrospective review of all patients with metastatic breast cancer treated with oxaliplatin at our hospital between February 2003 and November 2009. Patients were identified through electronic traceability of oxaliplatin administrations. Data from

patients with metastatic breast cancer were then extracted by oncologists. Baseline characteristics and detailed treatments (pattern of use, safety, activity) were recorded from patient charts by an oncologist and a pharmacist. Toxicity (grade >1) was assessed according to the National Cancer Institute Common Toxicity Criteria version 2.0. Activity was assessed according to tumor marker level and imaging. Overall survival was calculated from the date of initiation of oxaliplatin until the date of death.

Results

Thirty female patients (median age: 49, range, 34-68 years) treated by oxaliplatin for metastatic breast cancer between February 2003 and November 2009 were identified. Patients characteristics are listed in Table I. A total of 20/30 of the tumours were estrogen receptor-positive and 3/30 overexpressed the human epidermal growth factor receptor type 2 (HER2). Estrogen receptor and HER2 status were unknown for 6 and 11 of the breast tumors. The median number of organs with metastasis was two (range, 1-4), with 18/30 patients having liver metastases, 18/30 bone metastases, and 10/30 brain involvement. All patients had been pretreated for metastatic breast cancer (median number of previous lines: 3; range: 1-6). Fifty percent and 73% of patients, respectively, had received prior anthracyclines and taxanes for metastatic disease and 16/30 were given hormone therapy for advanced disease. Half of the patients (15/30) had undergone neoadjuvant or adjuvant chemotherapy.

Oxaliplatin was only given in association either with fluorouracil and folinic acid (n=23), or with gemcitabine (n=7). The most commonly used dose was 100 mg/m² given every other week, or every 3 weeks. As of December 15, 2009, the median duration of treatment was 4 months (range, 0.75-11 months). Discontinuations occurred due to disease progression (n=11), adverse effects (n=7), worsening condition (n=1) and patient request (n=1). Reasons were not mentioned for the remaining 9 patients.

Twelve (40%) patients presented side-effects related to oxaliplatin uses including hematotoxicity (n=8), gastrointestinal disorders (n=4) and neuropathies (n=2). No febrile neutropenia was encountered. Among patients evaluable for antitumoral activity (n=15), one patient with 4 metastatic sites achieved a complete response after 26 weeks of treatment and one patient with lung metastasis as a dominant site demonstrated a partial response after 12 weeks of treatment. Most of the patients (57%) continued to be treated by chemotherapy after oxaliplatin. Median overall survival for evaluable patients (n=15) was 10 months (range, 1-51 months).

Discussion

Oxaliplatin was used here off-label in patients highly pretreated for metastatic breast cancer. Most of the patients had received anthracycline- and taxane-containing regimens

Table I. Baseline characteristics of the study patients (n=30).

Characteristic	
Female gender, n (%)	30 (100)
Median age, years (range)	55 (45-68)
Primary tumour type	
Ductal carcinoma	19
Lobular carcinoma	4
Other	2
Missing data	5
Number of organs involved	
1	6
2	11
3	9
>4	4
Median	2
Range	1 to 4
Metastatic site	
Liver	18
Bone	18
Central nervous system	10
Lung	9
Lymph nodes	10
Cutaneous	3
Other	3
Prior chemotherapies for metastatic disease	
1	1
2	5
3	5
>3	19
Median	3
Range	1 to 6
Prior anthracycline-based chemotherapy for metastatic disease, number (%)	15 (50)
Taxane-based	22 (73)

that constitute the approved basis of treatment for metastatic disease. Oxaliplatin was not given as single agent, being combined either with fluorouracil or gemcitabine. There is no standard of care for pretreated metastatic breast cancer; patients may be offered other approved drugs for breast cancer, alone or in combination, they may be enrolled in clinical trials, or prescribed anticancer agents used off-label (*i.e.* used for a different type of cancer from that for they are approved). Regarding the general cancer population on chemotherapy, patients with breast cancer represent an important fraction of patients with off-label prescriptions. This is due mostly to the high prevalence of the disease because off-label drug use for breast cancer is low due to the availability of numerous approved drugs including cytotoxic agents, hormone therapy, anti-HER2 therapies and the antiangiogenic drug bevacizumab (1). We selected oxaliplatin because we found that it was the major anticancer agent used

in the off-label treatment of breast cancer in the years 2002 and 2003 (2, 3). Oxaliplatin has a high potential for off-label use because, like irinotecan, it is one of the rare, potentially broad-spectrum, cytotoxic agents that paradoxically remains approved for only one type of tumor. Since 2001, oxaliplatin alone or in combination with other anticancer agents has been evaluated in several studies of pretreated metastatic breast cancer and has demonstrated some activity at various doses (85-130 mg/m²) and schedules (4-13). However, it has not been the subject of a new application from the manufacturer. It is unlikely that oxaliplatin will be indicated for pretreated breast cancer since it is now available in numerous generic forms. Additionally, new therapeutic options have emerged with the recent approval in the USA of the cytotoxic agents ixabepilone and eribulin.

In our study, the response rate for evaluable patients was low (2/15), similar to the rate reported in clinical trials evaluating oxaliplatin for pretreated breast cancer (range: 7.5-35%) (4-13). It has to be stressed that one-third of the population had brain metastasis that generally constitutes an exclusion criterion in clinical trials. Side-effects imputable to oxaliplatin-containing combinations were common, resulting in the discontinuation of treatment in 7 patients. Interestingly, this off-label treatment was not the last alternative in almost one half of this highly pretreated population, emphasizing potential survival after progression. Regarding the limitations of this retrospective chart review, missing data have precluded an exhaustive evaluation of treatment discontinuations and clinical response.

In conclusion, oxaliplatin was used off-label combined with other anticancer agents in patients heavily pretreated for metastatic breast cancer. Given the modest activity and the significant toxicity, oxaliplatin use was of little worth in our population. This off-label treatment was not the last therapeutic option for most of these patients.

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