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ORIGINAL ARTICLE

A multicenter phase II trial of docetaxel plus gemcitabine as salvage treatment in anthracycline- and taxane-pretreated patients with metastatic breast cancer

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Abstract
Objective To evaluate the docetaxel–gemcitabine (DG) combination administered every 2 weeks as salvage therapy in anthracycline- and taxane-pretreated patients with metastatic breast cancer (MBC).
Patients and treatment Thirty women with MBC who had disease progression after chemotherapy with anthracyclines, or anthracyclines and taxanes were treated with docetaxel 50 mg/m^2 and gemcitabine 1,500 mg/m^2 on days 1 and 14 in cycles of 28 days. All patients had received prior anthracyclines, and fourteen (46.6%) had also received prior taxanes. All patients were evaluable for toxicity and 24 for response to treatment.
Results Complete response occurred in four (13.3%) patients and partial response in 10 (33.3%) for an overall response rate of 46.7% (95% CI 28.8–64.5). Seven patients (23.3%) had stable disease and nine (30%) progressive disease. Of the 14 patients previously treated with both anthracyclines and taxanes, seven (50%) responded. The median duration of response was 4.8 months (range 1.9–15.3), the median time to disease progression 6.6 months (range 0.5–16.9) and the median overall survival 16.8 months (range 1.3–53.2). There was no treatment-related toxic death. Neutropenia was the only grade 4 toxicity occurring in three (10%) patients. None of them developed neutropenic fever. Grade 3 thrombocytopenia occurred in two (6.7%) patients. Non-hematological toxicities were manageable.
Conclusion The DG combination administered biweekly is very well tolerated and effective in anthracycline- and taxane-pretreated patients with MBC. A previous treatment with taxanes does not preclude a good clinical response to this regimen.

Keywords Docetaxel · Gemcitabine · Metastatic breast cancer · Anthracycline

Introduction

Breast cancer is the most commonly diagnosed cancer in women in the United States, accounting for the 26% of all cancers in women [1]. Despite progress achieved in screening and management of early breast cancer, 25–30% of patients with negative axillary lymph nodes and more than two-thirds of those with axillary lymph node involvement at the time of diagnosis will have recurrent and/or metastatic disease within a decade after surgery and will subsequently die [2].

Metastatic breast cancer (MBC) remains an incurable disease with a poor prognosis [3] and only temporarily can be controlled with endocrine therapy or chemotherapy; therefore, palliation of symptoms and prolongation of high-quality life are important therapeutic goals in this setting [4]. To achieve these goals, the adverse events of palliative chemotherapy should be predictable, reversible and manageable [1]. In addition, treatment choice depends on

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several other factors including both patients' parameters (age, menopausal status and personal preference) and tumor and disease characteristics (relapse site and extend of disease, tumor hormone receptor status, tumor expression of the human epidermal growth factor receptor 2 [HER2], disease-free interval and prior treatment exposure) [1].

Anthracyclines and taxanes are commonly used drugs for the treatment of patients with recurrent or/and MBC, irrespectively of the hormone receptor status [1]. Resistance to anthracyclines and taxanes has been defined clinically as disease recurrence or progression occurring within 6–12 months of completing adjuvant or neoadjuvant treatment using these drugs or disease progression occurring during treatment or within 3–6 months after the treatment with these agents in the metastatic setting [5, 6].

Gemcitabine is a deoxycytidine-analog antimetabolite that inhibits DNA synthesis and has shown activity in a variety of solid tumors, good toxicity profile and non-overlapping toxicity with other chemotherapeutic drugs [7]. As a single agent, gemcitabine yields response rates ranging from 14 to 37% as first-line treatment for advanced breast cancer and 12–30% as salvage therapy for patients previously treated with anthracyclines and/or taxanes [8]. The pharmacodynamics, efficacy and good toxicity profile of gemcitabine make it an ideal agent for polychemotherapy combinations, especially with platinum derivates, vinorelbine and taxanes [7].

Docetaxel is a semisynthetic taxane acting through disruption of mitosis, promoting microtubule assembly and suppressing microtubule depolymerisation [9]. Regimens using gemcitabine and taxanes yielded superior efficacy over docetaxel alone in terms of overall survival with manageable treatment-related adverse events [10].

The rationale for combining gemcitabine and docetaxel in MBC include (1) their distinct mechanisms of action; (2) high levels of single agent activity in advanced breast cancer; and (3) encouraging results of phase II trials evaluating this combination in the first- and second-line setting. Previous studies conducted by our Cooperative Group have demonstrated that the combination of docetaxel and gemcitabine is an active chemotherapy regimen in patients with MBC both in the front-line and in second-line setting [4, 9]. In addition, Alexopoulos et al. [11] clearly demonstrated that the docetaxel–gemcitabine combination is an effective regimen in patients with docetaxel-refractory or docetaxel-resistant MBC. In all these studies, the toxicity profile was manageable and compared favorably with that of other regimens [4, 9, 11].

The treatment for recurrent and resistant MBC remains a major clinical challenge, with clinicians treating an ever-increasing population of women with anthracycline- and/or taxane-resistant disease. The current phase II trial was designed in order to evaluate the activity and tolerability of a new biweekly schedule of docetaxel and gemcitabine combination as salvage treatment in anthracycline- and/or taxane-pretreated women with MBC.

Patients and methods

Eligibility

Women aged >18 years with histologically confirmed MBC, failing prior chemotherapy in the adjuvant or metastatic setting with anthracyclines, or anthracyclines and taxanes (disease recurrence occurring while on therapy or within 6–12 months of completing adjuvant or neoadjuvant therapy or within 3–6 months of the last dose for MBC), were eligible. Patients were required to have measurable disease, HER2-negative disease (score 0–1 by immunohistochemistry of FISH negative), adequate bone marrow (absolute neutrophil count $\geq$1,500/μl, platelet count $\geq$100,000/μl), liver (total bilirubin level $\leq$1.5 mg/dl, AST $\leq$ 3 times the upper limit of normal) and renal function (serum creatinine concentration $\leq$1.5 mg/dl), and a World Health Organization (WHO) performance status (PS) of 0–2. Prior radiation therapy was permitted if less than 25% of active bone marrow was treated. Patients were ineligible if they had evidence of central nervous system (CNS) metastasis; active infection unless adequately treated; secondary primary malignancies (except adequately treated basal cell carcinoma of skin and carcinoma in situ of uterine cervix). The protocol was approved by the Scientific and Ethics Committees of the participating institutions. All patients signed a written informed consent prior to study entry.

Treatment plan

Docetaxel (Taxotere; Sanofi Aventis Pharma, Collegeville, USA) was given at a dose of 50 mg/m^2 (in 250 ml 0.9% normal saline) by intravenous (IV) infusion over 60 min followed by gemcitabine (Gemzar; Eli Lilly, Indianapolis, USA) 1,500 mg/m^2 (in 250 ml 0.9% normal saline) by IV infusion over 30 min on days 1 and 14 in cycles of 28 days. All patients were pre-medicated with oral dexamethasone (16 mg) 12, 8 and 1 h prior to docetaxel infusion and continued dexamethasone 8 mg b.i.d. for 2 days afterward. Anti-emetics were routinely used. Prophylactic granulocyte colony-stimulating factor was not used in the first cycle, but was allowed in subsequent cycles for patients who experienced either febrile neutropenia or grade 4 neutropenia.

Patients with objective (complete or partial) response had to receive 6 cycles (12 treatments) of chemotherapy; in the case of further tumor regression after the sixth chemotherapy cycle, 3 additional cycles had to be administered for a maximum of 9 cycles (18 treatments). Patients with stable disease, as their best response, had to receive up to 6 chemotherapy cycles (12 treatments). Patients with documented progressive disease or unacceptable drug toxicity and patients withdrawing their consent were taken off study. All toxicity was graded according to the National Cancer Institute Common Toxicity Criteria [12]. Evaluable for toxicity were all patients who received at least one cycle of treatment. The doses for both gemcitabine and docetaxel were reduced by 25% if dose-limiting toxicities occurred including febrile neutropenia, grade 4 neutropenia or grade 3–4 thrombocytopenia. Also, in cases of grade $\geq$3 non-hematological toxicity (mainly diarrhea, asthenia or neurotoxicity), a 25% reduction in the docetaxel dose was performed.

Response evaluation

Pretreatment assessment, including medical history, physical examination, PS evaluation, complete blood cell count with differential, serum chemistry and baseline tumor measurements (CT or MRI), was performed within 4 weeks of registration and subsequently after every 2 chemotherapy cycles. Patients were evaluated weekly for hematological toxicity except in cases of grade 4 or febrile neutropenia, where daily monitoring was performed. Standard evaluation by history, physical examination and routine laboratory tests was performed before each treatment administration.

Assessment of response was made clinically and radiologically after every two cycles or months of follow-up till evidence of disease progression. In responding patients, the response had to be confirmed 4 weeks later after the first response had been recorded. Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were scored using the criteria defined by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [13]. Duration of response was defined as the time from the date when the measurement criteria for complete or partial response were met until the date of the first observed disease progression (PD) or death as a result of any cause. Time to progression was determined by the interval between the initiation of therapy and the first date that disease progression was objectively documented. Overall survival was defined as the time from the date of study entry to the date of death as a result of any cause. The follow-up time was measured from the day of first treatment administration to last contact or death.

Statistical methods

This phase II study was designed to evaluate the efficacy in terms of response rate of DG regimen given in a biweekly schedule as salvage treatment in MBC. Secondary end points were overall survival and time to progression. The two-step Simon design of phase II trials was adopted in order to calculate the required number of patients [14]. Two levels of response rate as end points were used: P_0 the level of response below which pursuit of the therapy would be of no interest was set at 20% and P_1 a level above which there would be clinically relevant response was set at 50%. First-stage sample size was calculated to be 10 patients and maximum sample size 30 patients. All clinical data were centrally collected and analyzed (Clinical Trial Office, Department of Medical Oncology, University General Hospital of Heraklion, Crete, Greece) using the SPSS version 10.0 statistical software. Analysis was performed on an intent-to-treat basis. Survival curves were plotted according to the method of Kaplan–Meier and tested for differences by using the long-rank test [15]. All tests were two-sided and considered significant when the resulting P value was $\leq$0.05.

Results

Patients' characteristics

Between 26/8/2002 and 12/4/2007, 30 patients with MBC were enrolled. All patients were evaluable for toxicity and 24 for response to treatment. The reasons why 6 patients were not evaluable for response were the following: patient's refusal to continue therapy before the first response evaluation ($n = 3$), lost to follow-up ($n = 1$), protocol violation ($n = 1$) and impossible intravenous therapy due to poor venous access ($n = 1$). All these patients were considered as progressors in the intention-to-treat analysis.

The patients' median age was 57.5 years, 93.3% had a PS of 0–1, 90% were postmenopausal, and most of them (66.7%) had a ductal infiltrating adenocarcinoma. Sixteen patients (53.3%) had hormone-receptor-positive disease. Eighteen (60%) patients had previously received $\geq$2 lines of chemotherapy for metastatic disease. All patients had received prior anthracyclines and 14 (46.6%) prior taxanes for either early or metastatic disease. Eight (26.7%) and two (6.7%) women had anthracycline- and taxane-refractory disease. The median time since the last exposure to chemotherapy was 7.1 months (range 0.5–50.0). Twenty-eight (93.3%) patients had visceral disease, including 13 (43.3%) with lung, 18 (60%) with liver metastasis and nine (30%) with both. Fourteen (46.7%) patients had also bone

Table 1 Demographic data

	N (%)
Patients enrolled	30
Age	
Median (min–max)	57.5 (32–75)
Performance status	
0	12 (40)
1	16 (53.3)
2	2 (6.7)
Menopausal status	
Premenopausal	3 (10)
Postmenopausal	27 (90)
Histology	
Ductal	20 (66.7)
Lobular	1 (3.3)
Ductal–lobular	3 (10)
Other	1 (3.3)
Unknown	5 (16.7)
Stage	
IIIB	2 (6.7)
IV	28 (93.3)
Line of therapy	
2	12 (40)
≥3	18 (60)
Type of prior taxane (15 pts)	
Docetaxel	10 (66)
Paclitaxel	3 (20)
Both	2 (13)
Interval from previous chemo (median, min–max)	7.1mo (0.5–50.0)
Hormone receptor status	
ER+/PR+	9 (30.0)
ER+/PR−	7 (23.3)
ER−/PR+	–
ER−/PR−	6 (20.0)
Unknown	8 (26.7)
No. of organs involved	
1	17 (56.7)
2	9 (30)
≥3	4 (13.3)
Organs involved	
Lung and Pleura	20 (66.6)
Lymph nodes	9 (30.0)
Liver	18 (60)
Bones	14 (46.7)
Skin	1 (3.3)
Other	4 (13.3)

involvement, and only two of them (6.6%) had only bone metastases. Patients' characteristics are presented in Table 1.

Table 2 Response to treatment according to hormone receptor status

	ER and/or PR positive $N = 16$	ER and PR negative $N = 6$
CR + PR ($n = 11$)	8 (50.0)	3 (50.0)
SD + PD ($n = 11$)	8 (50.0)	3 (50.0)

Treatment administration

A total of 223 cycles were administered during the study. The mean number of cycles per patient was 7.0 (range 1–9). The median interval between cycles was 16 days (range 14–34). Sixteen of 30 patients (53.3%) completed treatment as per protocol. Dose reductions were required in five (2.2%) cycles. Reasons for dose reductions were hematological ($n = 4$ cycles) and non-hematological ($n = 1$ cycle) toxicity. Treatment was delayed in 53 (23.8%) cycles for the following reasons: hematological toxicity ($n = 8$ cycles), non-hematological toxicity ($n = 1$ cycle) and for reasons unrelated to treatment (e.g., late admissions due to patients' request or pending imaging studies for response evaluation; $n = 44$ cycles). The mean delivered dose intensity for gemcitabine was 650 mg/m^2/week and for docetaxel 21.8 mg/m^2/week, corresponding to 86.7 and 87% of the protocol planned dose, respectively.

Treatment efficacy

In an intention-to-treat analysis, there were four (13.3%) complete (CRs) and 10 (33.3%) partial (PRs) responses for an overall response rate of 46.7% (95% CI 28.8–64.5). Additionally, seven patients (23.3%) had stable disease (SD) and nine (30%) progressive disease (PD). Among the 14 patients who had previously treated with both anthracyclines and taxanes, seven (50%) achieved an objective response (CR or PR). The median duration of response was 4.8 months (range 1.9–15.3) and the median time to disease progression 6.6 months (range 0.5–16.9). Response to treatment according to hormone receptor status is shown in Table 2.

After a median follow-up time of 31.5 months (range 1.3–53.2), 22 patients (73.3%) had died mainly from disease progression ($n = 21$ patients); one patient died from reasons unrelated to her disease. The median overall survival was 16.8 months (range 1.3–53.2), and the estimated probability of 1-year survival for the entire group of patients was 66.2%.

Treatment toxicity

All patients were assessed for toxicity. No toxic death occurred. Table 2 summarizes the hematological and

non-hematological toxicities for all patients. No treatment was discontinued due to toxicity. Neutropenia was the only NCI-CTC grade 4 toxicity occurring in three (10%) patients, while grade 3 neutropenia occurred in five (16.7%) patients. None of them developed neutropenic fever. Grade 3 thrombocytopenia was documented in two (6.7%) patients, but no platelet transfusions were required. Non-hematological toxicities were usually mild and manageable; nausea, vomiting and mucocities were the main grade 3 toxicities. Prophylactic administration of granulocyte colony-stimulating factor was necessary in three patients who developed grade IV neutropenia, while there was no hospital admission due to toxicity.

Table 3 Adverse events possibly or probably related to study treatment

Toxicity	No. of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	3 (10)	4 (13.3)	5 (16.7)	3 (10)
Anemia	20 (66.7)	7 (23.3)		
Thrombocytopenia	10 (33.3)	1 (3.3)	2 (6.7)	
Nausea/vomiting	13 (43.3)	2 (6.7)	2 (6.7)	
Diarrhea	3 (10)	2 (6.7)		
Constipation	2 (6.7)	2 (6.7)		
Mucositis	2 (6.7)	1 (3.3)	1 (3.3)	
Neurotoxicity	3 (10)			
Fatigue	3 (10)	9 (30)		
Edema/fluid retention	1 (3.3)			
Hand–foot syndrome		1 (3.3)		

Discussion

As many as 30% of women diagnosed with early breast cancer will eventually progress to or relapse with locally advanced or MBC [1]. Patients with MBC previously treated with anthracyclines for advanced disease are usually refractory to any further treatment with anthracyclines and in general have a poor prognosis. Therefore, new drugs or new combinations of drugs are needed. The dynamic balance between chemotherapy-induced side effects and benefits attributable to relief of cancer-related symptoms must be carefully considered [8]. At the present time, available evidence does not provide definite guidance regarding the optimal chemotherapy agents and combinations in anthracycline- and taxane-pretreated patients with MBC [16]. Five agents are currently approved for use in previously treated patients with MBC: taxanes (paclitaxel and docetaxel), capecitabine, gemcitabine, vinorelbine and, in the USA, ixabepilone, eribulin and nab-paclitaxel [1, 17–19].

The combination of gemcitabine–paclitaxel is indicated as first-line treatment for patients with MBC who relapsed after anthracycline-containing adjuvant chemotherapy as well as for anthracycline-naïve patients who cannot receive anthracyclines due to co-morbidities [20]. FDA approval followed the results of a phase II trial of Albain et al. involving 529 patients who had relapsed after adjuvant treatment with anthracyclines [1]. In that trial, the gemcitabine plus paclitaxel combination achieved higher ORRs (41.4 vs. 26.2%; $P < 0.001$), longer median TTP (6.1 vs. 4 months; $P < 0.001$) and longer OS (18.6 vs. 15.8 months; $P < 0.049$) than paclitaxel alone [21].

The clinical activity of the gemcitabine plus docetaxel combination in advanced breast cancer has been tested in several phase II studies with response rates ranging from 36 to 79% (Table 3). Palmeri et al. [22] using a weekly schedule of docetaxel and gemcitabine administration as first-line treatment for 58 MBC patients found an ORR of 64.3%. Laufmann et al. [23] evaluated the efficacy and safety of monthly docetaxel combined with weekly gemcitabine as first- or second-line treatment in 39 patients with MBC and found an ORR of 79% and manageable hematological toxicity. The activity of the docetaxel–gemcitabine combination in women with disease progression after initial chemotherapy for MBC was investigated in two other multicenter phase II trials of Mavroudis et al. [24] and Kornek et al. [2] with an ORR of 54 and 60.5%, respectively. At the 2005 Annual ASCO Meeting, Chan et al. [26] presented a phase III study comparing the combination of gemcitabine–docetaxel with that of capecitabine–docetaxel as first- and second-line therapy in breast cancer patients pretreated with anthracyclines. Three hundred and five patients were randomized to receive gemcitabine and docetaxel (GD), or capecitabine and docetaxel (CD) every 21 days. The best overall response rate was 32% in both arms, whereas the time to treatment failure was 4.24 and 4.07 months, respectively. Progression-free survival, the primary end point of the study, was 35 weeks in both treatment arms [26].

In the current phase II trial, the combination of docetaxel and gemcitabine was evaluated in 30 MBC patients pre-treated with either anthracycline or anthracycline and taxanes. The combination was associated with an ORR of 46.7%, which is better than that reported in studies evaluating single agent gemcitabine. Indeed, phase II studies with single agent gemcitabine have reported 0% objective responses in patients previously treated with both an anthracycline- and a taxane-containing regimen, whereas in another study, an ORR of 25% has been documented in patients treated in the first- or second-line setting [10]. Conversely, the efficacy results reported in the current study are quite similar to those obtained with single agent docetaxel (18–64%) [27]. It seems noteworthy that the

Table 4 Phase II trials of docetaxel–gemcitabine combination

Author	Study	Patients	Schedule of treatment	ORR (%)	Median survival (months)
Palmeri [19]	Phase II 1st, 2nd line	58	Docetaxel 35 mg/m^2 and gemcitabine 800 mg/m^2 i.v. on days 1, 8, 15 every 4 weeks	64.3	22.1
Foutzilas [26]	Phase II 1st, 2nd line	40	Docetaxel 75 mg/m^2 on day 1 and gemcitabine 1,000 mg/m^2 on days 1 and 8, every 3 weeks	35	12
Mavroudis [21]	Phase II 1st, 2nd line	52	Gemcitabine 900 mg/m^2 on day 1 and day 8 and docetaxel 100 mg/m^2 on day 8, every 3 weeks	54	15
Laufman [20]	Phase II 1st, 2nd line	39	Gemcitabine 800 mg/m^2 days 1, 8, 15 and docetaxel 100 mg/m^2 on day 1, every 4 weeks	79	24.5
Kornek [22]	Phase II 1st, 2nd line	52	Gemcitabine 1,500 mg/m^2 and docetaxel 50 mg/m^2, both administered on days 1 and 15 every 4 weeks	60.5	
Alexopoulos [9]	Phase II 1st, 2nd line	50	Gemcitabine 900 mg/m^2 on days 1 and 8 plus docetaxel 100 mg/m^2 on day 8, every 3 weeks	46	
O' Shaughnessy [28]	Phase II, 1st line	46	Docetaxel 30 mg/m^2 and gemcitabine 800 mg/m^2 on days 1, 8, and 15 every 4 weeks	39	15.8

therapeutic efficacy was not influenced by adverse prognostic factors such as multiple lines of prior therapy, presence of visceral disease and multiple metastatic sites. Interestingly, half of the 14 patients previously treated with taxanes achieved an objective response to DG regimen. This observation strongly suggests that the efficacy of the DG combination after taxane failure in patients with MBC might be attributed to an in vivo synergism between the two drugs (Table 4).

A major advantage of the DG combination is its moderate and manageable toxicity, which could be attributed to the bi-weekly administration schedule. Compared with the 3-weekly administration of docetaxel and gemcitabine, the biweekly schedule has less hematological toxicity, while the asthenia and the docetaxel-related fluid retention are observed in a significantly lower intensity. On the other hand, despite less febrile neutropenia, fatigue and general malaise are common reasons that lead to patient withdrawals when the weekly docetaxel is used [28]. At the same time, the reduction in hematological toxicity for the weekly docetaxel schedule compared with the 3-weekly schedule must be considered from a balanced perspective as it requires an increased number of clinic visits for therapy [29]. In patients with early breast cancer, Sparano et al. [30] reported a randomized phase 3 trial comparing weekly versus 3-weekly docetaxel or paclitaxel after doxorubicin plus cyclophosphamide: A higher 5-year disease-free survival rate in the 3-weekly docetaxel arm (81.2 vs. 77.6%) was observed. In addition, the European phase III trial, comparing gemcitabine plus docetaxel with capecitabine plus docetaxel, which was mentioned previously, showed similar efficacy results, with more toxicity in the capecitabine arm [26].

In the present phase II trial, the incidence of grade 3 or 4 neutropenia was limited in 10 and 16.7% of patients, respectively, while there was no episode of febrile neutropenia. Moreover, grade 3 thrombocytopenia, nausea/vomiting and mucosity were reported in 16.7% of patients, and other toxicities were mild and infrequent. Treatment compliance was excellent with median delivered dose intensities of 86.7 and 87% of the protocol-planned doses for gemcitabine and docetaxel, respectively, with 24% of chemotherapy cycles delayed because of hematological and non-hematological toxicity.

Although there is no multicenter, randomized phase III trial comparing the two schedules, it seems that the biweekly administration of gemcitabine and docetaxel in MBC is an interesting alternative compared to a 3-week schedule whenever hematological toxicity is the main clinical concern. Murialdo et al. [31] recently reported a phase II trial of biweekly docetaxel and gemcitabine regimen in HER2-negative and anthracycline-pretreated MBC, which showed that this schedule of administration is well tolerated and active as first line in anthracycline-pretreated women with MBC. Further investigation into phase III studies is required.

In conclusion, the biweekly schedule of DG combination represents a valuable therapeutic option for the treatment of heavily pretreated MBC patients since it is active and well tolerated. Of course, the best choice of salvage therapy depends on the specific clinical scenario, and for most patients with slow-growing and non life-threatening asymptomatic disease, single agent treatment might be the preferred option. However, for symptomatic patients and especially for those with aggressive and extensive disease who have still in good performance status and have already

failed anthracyclines and even taxanes, the biweekly administration schedule of DG combination represents a reasonable option. The need for active, efficacious and non-cross resistant regimens, confirmed in randomized trials conducted in a selected population of pretreated patients, is therefore of the utmost importance.

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