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## DEXAMETHASONE, GRANISETRON, OR BOTH FOR THE PREVENTION OF NAUSEA AND VOMITING DURING CHEMOTHERAPY FOR CANCER

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**Abstract Background.** Serotonin-receptor antagonists seem to be as effective as corticosteroids in preventing emesis induced by moderately emetogenic antineoplastic agents. We compared the antiemetic effect of a combination of granisetron and dexamethasone with that of granisetron or dexamethasone administered alone.

**Methods.** From December 1992 to January 1994, 428 consecutive patients who were to receive moderately emetogenic chemotherapy for the first time (600 to 1000 mg of cyclophosphamide per square meter of body-surface area,  $\geq 50$  mg of doxorubicin per square meter,  $\geq 75$  mg of epirubicin per square meter, or  $\geq 300$  mg of carboplatin per square meter, alone or in some combination) were enrolled in a double-blind, randomized, multicenter study evaluating the efficacy and toxicity of three antiemetic regimens. The following antiemetic regimens were used: 8 mg of dexamethasone given intravenously before chemotherapy plus 4 mg given orally immediately before chemotherapy and then every six hours for a total of four doses, 3 mg of granisetron given intravenously be-

fore chemotherapy, or a combination of granisetron and dexamethasone given in the doses used for the single-drug regimens.

**Results.** We evaluated 408 patients (136 receiving dexamethasone, 137 receiving granisetron, and 135 receiving both drugs). In the first 24 hours after chemotherapy, complete protection from vomiting and complete protection from nausea were achieved in 70.6 and 55.1 percent, respectively, of the patients receiving dexamethasone, in 72.3 and 48.2 percent of those receiving granisetron, and in 92.6 and 71.9 percent of those receiving granisetron combined with dexamethasone ( $P < 0.001$  for all comparisons). Patients who received granisetron alone had less protection from delayed vomiting and nausea than those who received dexamethasone alone or the two drugs combined. All the regimens were equally well tolerated.

**Conclusion.** Granisetron combined with dexamethasone was the most effective regimen for the prevention of emesis induced by moderately emetogenic chemotherapy. (N Engl J Med 1995;332:1-5.)

NAUSEA and vomiting are among the most distressing side effects of chemotherapy for cancer, but the best way to prevent these symptoms is unclear. In randomized comparative clinical trials, high and repeated doses of corticosteroids have consistently been shown to be effective and well-tolerated antiemetic agents; in patients undergoing moderately emetogenic chemotherapy, dexamethasone or methylprednisolone is more effective or better tolerated (or both) than the phenothiazines or benzamides.<sup>1-8</sup> Antagonists to serotonin (5-hydroxytryptamine<sub>3</sub> [5-HT<sub>3</sub>]) receptors are also effective antiemetic agents when used with such chemotherapeutic regimens.<sup>9-14</sup> However, only three published studies have compared a 5-HT<sub>3</sub> antagonist with high-dose steroids.<sup>12-14</sup>

Jones et al. found that ondansetron and dexamethasone were equally effective in controlling acute nausea and vomiting but that dexamethasone had an advantage in the control of delayed nausea.<sup>12</sup> In contrast, the two other studies found that granisetron was more ef-

fective and less toxic than dexamethasone combined with a phenothiazine.<sup>13,14</sup> However, in those two studies dexamethasone was administered only in a single intravenous dose before chemotherapy, and its use in combination with phenothiazines is questionable, since the efficacy of phenothiazines in the prevention of emesis induced by moderately emetogenic chemotherapy has not been confirmed. Therefore, it is not clear whether corticosteroids in high doses have an advantage over any 5-HT<sub>3</sub> antagonist in controlling nausea and vomiting, or whether a combination of a 5-HT<sub>3</sub> antagonist and dexamethasone can improve the control of acute and delayed vomiting and nausea.

To answer these questions, we conducted a prospective, randomized, double-blind study comparing the antiemetic activity and tolerability of granisetron alone, dexamethasone alone, and the combination of granisetron and dexamethasone in patients receiving moderately emetogenic chemotherapy.

## METHODS

### Patients

From December 1992 to January 1994, consecutive adult patients scheduled to receive moderately emetogenic chemotherapy for the first time were enrolled in the study. The patients were to receive cy-

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clophosphamide (600 to 1000 mg per square meter of body-surface area), doxorubicin ( $\geq 50$  mg per square meter), epirubicin ( $\geq 75$  mg per square meter), or carboplatin ( $\geq 300$  mg per square meter), either alone or in some combination.

The criteria for exclusion before randomization were the presence of nausea and vomiting or the use of antiemetic agents during the 24 hours before the administration of chemotherapy, a severe concurrent illness other than neoplasia, epileptic seizures during the previous year, other causes of vomiting (e.g., gastrointestinal obstruction, central nervous system metastases, or hypercalcemia), concurrent treatment with corticosteroids (unless given as physiologic supplements) or benzodiazepines (unless given at night for sedation) or radiotherapy, and a white-cell count under 3000 per cubic millimeter or a platelet count under 70,000 per cubic millimeter. Also excluded from the study were patients with a Karnofsky performance score below 40; pregnant women; patients in whom the administration of dexamethasone was contraindicated; patients scheduled to receive dacarbazine, cisplatin, ifosfamide, cytarabine, or mechlorethamine on the day of chemotherapy and any cytotoxic agent from day 2 to day 5, excluding etoposide, teniposide, and vincristine; patients with marked hepatic dysfunction (e.g., a liver-function value more than four times the upper limit of normal), and patients who were unwilling or unable to comply with the protocol.

A 10 percent error in the dose of administered antineoplastic agents was allowed for the analysis of clinical efficacy. Patients receiving less than 540 mg of cyclophosphamide per square meter, less than 45 mg of doxorubicin per square meter, less than 67.5 mg of epirubicin per square meter, or less than 270 mg of carboplatin per square meter were evaluated only according to the intention-to-treat principle.

### Design of the Study

A comparative study with a randomized, double-blind parallel design was conducted at 23 medical or gynecologic oncology divisions in Italy. The study was conducted according to the provisions of the Declaration of Helsinki and was approved by the ethics committee of each participating institution; all patients gave written informed consent.

The number of patients to be enrolled in the trial was calculated on the assumption that complete control of acute vomiting would be achieved in at most 65 percent of patients treated with dexamethasone, in at least 75 percent of those receiving granisetron, and in at least 85 percent of those treated with granisetron plus dexamethasone. An overall P value (two-sided)  $\leq 0.05$  was considered to indicate statistical significance. A total enrollment of 387 patients was required for the study to have a 90 percent probability of detecting a significant difference.

### Antiemetic Therapy

With the use of a block-balanced randomization list (12 patients per block), patients were randomly assigned to receive one of three antiemetic treatments in a blinded fashion in the first 24 hours after the administration of chemotherapy. The first treatment consisted of 20 ml of saline given as an intravenous infusion over a period of 5 minutes 20 minutes before chemotherapy, followed by 8 mg of dexamethasone (Decadron phosphate, Merck Sharp & Dohme, Rome) diluted in 100 ml of saline and administered as an intravenous infusion over a period of 15 minutes. Immediately before the start of chemotherapy, 4 mg (one capsule) of dexamethasone (Organon Laboratories, Cambridge, United Kingdom) was administered, and this dose was repeated every six hours for a total of four doses.

The second treatment consisted of 3 mg of granisetron (Kytril, SmithKline Beecham, Harlow, Essex, United Kingdom) in 20 ml of saline given as an intravenous infusion over a period of 5 minutes 20 minutes before chemotherapy, followed by 100 ml of saline administered as an intravenous infusion over a period of 15 minutes. A placebo capsule was administered immediately before the start of chemotherapy and then every six hours for a total of four doses.

The third treatment consisted of 3 mg of granisetron in 20 ml of saline given as an intravenous infusion over a period of 5 minutes 20 minutes before chemotherapy, followed by 8 mg of dexamethasone diluted in 100 ml of saline administered as an intravenous infusion over a period of 15 minutes. Immediately before the start of chemothera-

py, 4 mg (one capsule) of dexamethasone was administered, and this dose was repeated every six hours for a total of four doses.

To ensure that the oral treatment (placebo or dexamethasone) could not be identified, the tablets were put in identical capsules. Food intake was not permitted until six hours after the administration of chemotherapy. After the completion of the assigned treatment, the patients received no further antiemetic prophylaxis.

### Clinical Assessment

Episodes of nausea and retching or vomiting were recorded by the patients on diary cards for the first 24 hours after chemotherapy (acute effects) and for the following four days (delayed effects). An episode of vomiting was defined as a single instance of vomiting or retching or continuous vomiting or retching. A vomiting episode was considered to have ended when retching or vomiting had ceased for at least one minute. Complete protection was defined as the absence of vomiting episodes, major protection as one or two episodes, and failure of the treatment as three or more episodes. Complete or major protection was considered to indicate successful treatment.

Nausea was graded according to the following scale: 0 none, 1 mild (did not interfere with normal daily life), 2 moderate (interfered with normal daily life), and 3 severe (required the patient to be bedridden). The absence of nausea was defined as complete protection. The intensity of delayed nausea was recorded as the worst nausea experienced during days 2 through 5. The time to the first episode of vomiting or the beginning of any nausea was defined as the interval between the start of chemotherapy and the beginning of the vomiting episode or nausea.

Adverse events other than episodes of vomiting or nausea were recorded on the diary cards by the patients in response to a general question. Any adverse event, as well as the presence of nausea, retching, or vomiting, from day 6 to the start of the subsequent cycle of chemotherapy was also recorded.

A patient who had three or more vomiting episodes or severe nausea (or both) could receive metoclopramide (20 mg) intramuscularly during the first 24 hours after chemotherapy and dexamethasone (8 mg) intramuscularly during days 2 through 5, with the dose repeated as needed.

### Statistical Analysis

Analyses of nausea and vomiting were performed separately for day 1 (acute effects) and days 2 through 5 (delayed effects). Fisher's exact test (generalized with the Freeman-Halton test) was used to evaluate the balance of prognostic factors and to compare the proportions with each adverse event among the three groups. Logistic linear models were used to compare the efficacy of the three antiemetic treatments (unifactorial analysis) as well as for multifactorial analyses; therefore, overall G tests and z-tests for the differences between the levels of factors and the interactions were used.

The mean number of vomiting episodes, the mean maximal intensity of nausea, and the mean time to the start of any nausea or vomiting were compared with the Kruskal-Wallis test; when a difference was significant, the pairwise comparison between groups was performed with the Wilcoxon rank-sum test.

### RESULTS

A total of 428 patients took part in the study, but 5 of them were lost to follow-up and 15 erroneously received oral cyclophosphamide (100 mg per square meter per day) for more than one day. Therefore, 408 patients were evaluated according to the intention-to-treat principle. The characteristics of the patients in the three treatment groups were similar (Table 1).

Data on 398 patients (132 receiving dexamethasone, 134 granisetron, and 132 dexamethasone plus granisetron) were evaluated for clinical efficacy; 10 patients were not evaluated because they used benzodiazepines (2 patients) or because the dose of antineoplastic agents differed by more than 10 percent from the protocol dose (8 patients).

**Table 1. Characteristics of 408 Patients Receiving Antiemetic Treatment with Dexamethasone, Granisetron, or a Combination of the Two Drugs.\***

CHARACTERISTIC	DEXAMETHASONE PLUS GRANISETRON		
	DEXAMETHASONE (N = 136)	GRANISETRON (N = 137)	DEXAMETHASONE PLUS GRANISETRON (N = 135)
Sex — no. of patients (%)			
Male	23 (16.9)	22 (16.1)	20 (14.8)
Female	113 (83.1)	115 (83.9)	115 (85.2)
Median age — yr	53	55	54
Age group — no. of patients (%)			
26–49 yr	50 (36.8)	46 (33.6)	48 (35.6)
50–64 yr	64 (47.1)	66 (48.2)	66 (48.9)
65–78 yr	22 (16.2)	25 (18.3)	21 (15.6)
Use of alcohol — no. of patients (%)†			
None or <7 U/wk	95 (69.9)	97 (70.8)	101 (75.9)
1–4 U/day or more	41 (30.1)	40 (29.2)	32 (24.1)
Karnofsky score — no. of patients (%)			
40–80	19 (14.0)	18 (13.1)	14 (10.4)
90–100	117 (86.0)	119 (86.9)	121 (89.6)
Treatment setting — no. of patients (%)			
Outpatient	115 (84.6)	115 (83.9)	123 (91.1)
Inpatient	21 (15.4)	22 (16.1)	12 (8.9)
Primary site of tumor — no. of patients (%)			
Ovary	7 (5.1)	6 (4.4)	7 (5.2)
Lung	21 (15.4)	23 (16.8)	20 (14.8)
Breast	101 (74.3)	104 (75.9)	105 (77.8)
Other	7 (5.1)	4 (2.9)	3 (2.2)
Chemotherapy — no. of patients (%)			
Cyclophosphamide	82 (60.3)	75 (54.7)	71 (52.6)
Epirubicin	22 (16.2)	23 (16.8)	24 (17.8)
Doxorubicin	17 (12.5)	18 (13.1)	20 (14.8)
Carboplatin	15 (11.0)	21 (15.3)	20 (14.8)

\*Numbers may not sum to 100 because of rounding.

†Data were not available for two patients. One unit of alcohol was defined as 150 ml of wine, 1 liter of beer, or 50 ml of distilled spirits.

Table 2 shows the data on acute nausea and vomiting according to the intention-to-treat principle. The combination of dexamethasone and granisetron was significantly more effective than dexamethasone alone and granisetron alone for the most important outcomes considered; dexamethasone alone and granisetron alone had similar effects. Complete protection from vomiting was achieved in 96 of the 136 patients receiving dexamethasone alone (70.6 percent), in 99 of the 137 receiving granisetron alone (72.3 percent), and in 125 of the 135 receiving dexamethasone plus granisetron (92.6 percent).

The treatment was successful (i.e., it provided complete or major protection) in 111 patients (81.6 percent) in the dexamethasone group, 113 (82.5 percent) in the granisetron group, and 131 (97.0 percent) in the group receiving both drugs (P<0.001). The numbers of treatment failures in the groups were 25, 24, and 4, respectively.

Forty patients had vomiting in the dexamethasone group, 38 in the granisetron group, and 10 in the dexamethasone–granisetron group. The median number of emetic episodes

in the three groups (4, 3, and 2, respectively) was lowest in the dexamethasone–granisetron group, but the difference was not significant. The median time to the first emetic episode was longer in the dexamethasone group (8.75 hours) than in the granisetron group (6.25 hours, P=0.03) but was not significantly different from the median time to the first episode in the dexamethasone–granisetron group (8.0 hours, P=0.26).

Complete protection from nausea was also achieved in a larger number of patients receiving dexamethasone plus granisetron (97 of 135, as compared with 75 of 136 in the dexamethasone group and 66 of 137 in the granisetron group; P<0.001). However, the intensity of nausea was similar in the three groups. The median time to the start of nausea was significantly shorter in the granisetron group (5.4 hours) than in the dexamethasone group (7.8 hours, P=0.03) or the dexamethasone–granisetron group (7.7 hours, P=0.02).

Complete protection from both nausea and vomiting (Table 2) was also achieved in a significantly larger number of patients treated with dexamethasone plus granisetron (95 of 135, as compared with 67 of 136 in the dexamethasone group and 59 of 137 in the granisetron group; P<0.001). A multifactorial analysis confirmed that the antiemetic treatment was the most important factor in complete protection from nausea and vomiting (data not shown) and that dexamethasone plus granisetron was significantly more effective than either drug alone. The proportions of patients with complete protection from vomiting and complete protection from nausea did not differ significantly between the granisetron and dexamethasone groups. The analysis of clinical efficacy (among 398 patients) led to similar results (data not shown).

We also evaluated delayed vomiting (occurring during days 2 through 5) in 403 patients (134 in the dexamethasone group, 134 in the granisetron group, and 135 in the dexamethasone–granisetron group). Five patients were not included in the analysis because of loss to follow-up after the first day (one patient) or incomplete data on the diary cards (four patients). Table 3 shows the results of this analysis. The proportion of patients with complete protection from vomiting, nausea, or both on day 2 (as well as the proportion with complete protection from nausea or both nausea and vomiting on day 3) was significantly higher in the dexamethasone–granisetron group and the dexamethasone group than in the granisetron group. On days 4 and 5, the efficacy of the three antiemetic treatments did not

**Table 2. Percentages of Patients with Complete Protection from Acute Nausea, Vomiting, or Both.**

COMPLETE PROTECTION	DEXAMETHASONE PLUS GRANISETRON			P VALUE*
	DEXAMETHASONE (N = 136)	GRANISETRON (N = 137)	DEXAMETHASONE PLUS GRANISETRON (N = 135)	
	<i>% of patients (95% confidence interval)</i>			
From vomiting	70.6 (62.9–78.3)	72.3 (64.8–79.8)	92.6 (88.2–97.0)	<0.001
From nausea	55.1 (46.7–63.5)	48.2 (39.8–56.6)	71.9 (64.3–79.5)	<0.001
From nausea and vomiting	49.3 (40.9–57.7)	43.1 (34.8–51.4)	70.4 (62.7–78.1)	<0.001

\*Calculated with the G test.

differ significantly. The proportions of patients with overall complete protection against delayed emesis were also significantly higher in the groups receiving dexamethasone alone or combined with granisetron.

When the overall data for days 1 through 5 were considered, the combination treatment resulted in a higher frequency of complete protection from vomiting (79.3 percent) than either drug alone (67.2 percent with dexamethasone and 61.9 percent with granisetron). The total number of rescue treatments administered during days 1 through 5 was also significantly lower among the patients who received dexamethasone plus granisetron (5 treatments) than among those who received dexamethasone alone (14 treatments,  $P=0.06$ ) or granisetron alone (22 treatments,  $P<0.001$ ). On days 1 through 5, complete protection from nausea (in 44.8 percent of the patients receiving dexamethasone, 31.3 percent of those receiving granisetron, and 48.9 percent of those receiving both drugs) and from both nausea and vomiting (42.5, 28.4, and 47.4 percent, respectively) was significantly more frequent in both dexamethasone groups. Moreover, severe nausea was seldom observed: only 11 of 69 patients in the dexamethasone–granisetron group (15.9 percent), 15 of 74 in the dexamethasone group (20.3 percent), and 21 of 92 in the granisetron group (22.8 percent) recorded severe nausea on at least one day.

The percentages of patients with nausea or vomiting (or both) from day 6 to the next cycle of chemotherapy were very small and did not differ significantly among the three groups (6.7 percent in the dexamethasone group, 7.5 percent in the granisetron group, and 5.9 percent in the dexamethasone–granisetron group).

No severe or unexpected adverse events were reported by the 423 patients (all those randomly assigned to a treatment group except patients lost to follow-up);

Table 3. Percentages of Patients with Complete Protection from Vomiting, Nausea, or Both on Days 2 through 5.

COMPLETE PROTECTION	DEXAMETHASONE PLUS GRANISETRON			P VALUE*
	DEXAMETHASONE (N = 134)	GRANISETRON (N = 134)	GRANISETRON (N = 135)	
	% of patients			
From vomiting				
Day 2	89.5	77.6	89.6	0.008
Day 3	92.5	88.8	85.2	0.16
Day 4	96.3	91.0	90.4	0.11
Day 5	98.5	94.0	94.8	0.13
Days 2–5	85.8	71.6	80.7	0.02
From nausea				
Day 2	62.7	42.5	64.4	<0.001
Day 3	63.4	47.0	60.7	0.02
Day 4	68.7	61.9	66.7	0.49
Day 5	82.8	74.6	79.3	0.26
Days 2–5	56.0	37.3	51.8	0.006
From nausea and vomiting				
Day 2	61.9	41.0	62.2	<0.001
Day 3	61.9	44.8	60.0	0.009
Day 4	67.9	60.4	65.9	0.42
Day 5	82.1	72.4	77.8	0.17
Days 2–5	54.5	34.3	51.1	0.002

\*Calculated with Fisher's exact test (generalized with the Freeman–Halton test).

Table 4. Adverse Events (Day 1).

ADVERSE EVENT	DEXAMETHASONE (N=141)	GRANISETRON (N=141)	DEXAMETHASONE PLUS GRANISETRON (N=141)	P VALUE*
			no. of patients	
Constipation	0	3	9	0.006
Headache	14	16	14	0.89
Heartburn	4	0	0	0.06
Asthenia	11	9	5	0.30
Epigastric pain	3	4	2	0.69
Nervousness	1	0	1	0.54
Elevated aminotransferase values	0	1	0	0.40
Hot flushes	1	0	6	0.03
Insomnia	0	1	1	0.54
Other	19	18	10	0.16
Total	53	52	48	0.80

\*Calculated with Fisher's exact test (generalized with the Freeman–Halton test).

Table 4 shows the data for day 1. Constipation and hot flushes were significantly more frequent among the patients receiving dexamethasone plus granisetron than among those receiving either drug alone. Differences in the numbers of patients who had constipation became more evident on days 2 through 5 (0 in the dexamethasone group, 14 in the granisetron group, and 19 in the dexamethasone–granisetron group) and from day 6 to the next cycle of chemotherapy (0, 1, and 9, respectively). On days 2 through 5, hot flushes were significantly more frequent in both dexamethasone groups (14 patients in the dexamethasone–granisetron group and 10 in the dexamethasone group, as compared with 2 in the granisetron group).

## DISCUSSION

This randomized controlled study compared the combination of a 5-HT<sub>3</sub> antagonist and dexamethasone with each drug alone in the prevention of acute and delayed vomiting and nausea in patients receiving moderately emetogenic chemotherapy. The combination of dexamethasone plus granisetron during the first 24 hours was shown to be more effective than either dexamethasone or granisetron alone.

The 20 percent higher frequency of complete protection from acute vomiting, nausea, or both with the combined drugs and the lower frequency of treatment failures with the combination (3 percent, vs. 18 percent with either drug used alone) are clinically relevant. Fewer patients had protection from nausea than protection from vomiting (72 percent vs. 93 percent in the group of patients receiving the combination of drugs), a finding also reported in other studies.<sup>9–14</sup>

Protection against delayed vomiting and nausea is also important. Delayed emesis (starting 24 hours after the administration of chemotherapy) can persist for at least 48 hours, and patients may thus require antiemetic therapy for several days. However, in patients receiving moderately emetogenic chemotherapy relatively good control of delayed emesis is possible with-

out any adjunctive treatment, at least in those patients who are adequately protected against acute vomiting. Therefore, we did not treat our patients for delayed vomiting and nausea, unless they needed rescue treatment. It is noteworthy that about 80 percent of the patients treated with dexamethasone or dexamethasone plus granisetron remained free of vomiting during days 2 through 5 and that about 50 percent of them did not have delayed nausea. In contrast, the granisetron-treated patients had less protection against delayed nausea.

The reason why antiemetic treatment provides better protection against vomiting than against nausea is not clear. There may be two kinds of nausea, one related to vomiting and the other unrelated, which differ in their responsiveness to treatment.<sup>15</sup> Furthermore, the apparent advantage of dexamethasone over the 5-HT<sub>3</sub> antagonists in providing protection against delayed nausea indicates separate mechanisms of acute and delayed nausea. The three antiemetic treatments were equally well tolerated. The pattern of side effects we saw reflected previous experience with the same drugs.

In conclusion, the combination of dexamethasone and granisetron provides effective prophylaxis in patients treated with moderately emetogenic chemotherapy. It is likely that these results also apply to other 5-HT<sub>3</sub> antagonists, but this supposition requires proof from further studies. Although the antiemetic treatment was restricted to the first 24 hours, it also provided protection from delayed vomiting. Whether protection from delayed nausea can be improved by prolonged administration of dexamethasone remains to be demonstrated. Our results indicate that for prophylaxis against vomiting and nausea in patients receiving moderately emetogenic chemotherapy, granisetron alone is not worthwhile, except when corticosteroids are contraindicated. Our findings suggest that even treatment with dexamethasone alone could be satisfactory and cheaper than treatment with dexamethasone plus granisetron; an economic evaluation of the two options would be interesting.

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#### APPENDIX

The Italian Group for Antiemetic Research includes the following principal investigators, investigators, and collaborating centers. *Principal investigators:* F. Roila (Medical Oncology Division, Policlinico Hospital, Perugia); E. Ballatori and V. De Angelis (Department of Internal Medicine and Public Health, University of L'Aquila, L'Aquila); M. Tonato (Medical Oncology Division, Policlinico Hospital, Perugia); E. Riva and M.T. Panza (Medical Department, SmithKline Beecham Italy, Milan); and A. Del Favero (Department of Internal Medicine and Oncological Sciences, University of Perugia, Perugia). *Investigators and collaborating centers:* Medical Oncology Division, Policlinico Hospital, Perugia: C. Basurto, G. Ciccarese, M.A. Palladino, A.M. Mosconi, P. Anastasi, and M. Picciafuoco; National Institute for Cancer Research, Genoa: E. Campora, S. Chiara, and R. Rosso; Department of Medical Oncology, Regina Elena Institute, Rome: F. Cognetti, V. Ferraresi, A. Fabi, R. Tonachella, and S. Cirulli; Medical

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