Docetaxel-Induced Lymphopenia in Patients with Solid Tumors

A Prospective Phenotypic Analysis

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BACKGROUND. The quantitative abnormalities of the different peripheral blood lymphocyte subsets during docetaxel administration were prospectively studied.
METHODS. Forty-six chemotherapy-naive patients with solid tumors were treated with docetaxel either in a 3 weekly (n = 33) or weekly (n = 13) schedule. Twenty patients with central nervous system (CNS) metastatic disease as the first clinical presentation of cancer and 35 patients with metastatic colorectal carcinoma treated with chemotherapy were enrolled as controls. The phenotype of peripheral blood lymphocytes was determined by indirect immunofluorescence using appropriate monoclonal antibodies and fluorescent-activated cell sorter analysis.
RESULTS. After the administration of the first docetaxel cycle, the absolute number of peripheral blood lymphocytes ($P < 0.005$), $CD3^+$ ($P < 0.01$), $CD4^+$ ($P < 0.01$), $CD8^+$ ($P < 0.01$), and $CD56^+$ ($P < 0.01$) but not $CD20^+$ ($P < 0.3$) cells was significantly decreased compared with the pretreatment values. Further treatment resulted in a further decrease of these lymphocyte subsets including $CD20^+$ cells ($P < 0.01$). Similarly, after the administration of the first weekly dose of docetaxel, the absolute number of total lymphocytes, $CD3^+$, $CD4^+$, and $CD8^+$ cells was decreased. The administration of the second weekly docetaxel dose resulted in a further decrease of $CD56^+$ ($P = 0.012$) and $CD20^+$ ($P = 0.007$) cells. The administration of either high dose corticosteroids in patients with CNS metastases or an irrelevant chemotherapy (CPT-11/5-FU) did not result in similar abnormalities. The discontinuation of docetaxel was associated with a recovery of $CD3^+$ and $CD4^+$ lymphocytes within a 3-month period. Eight (17%) patients developed nonneutropenic infections during docetaxel treatment.
CONCLUSIONS. Docetaxel has an important but reversible nonspecific lymphopenic effect that seems to be associated with an increased risk for nonneutropenic infections. ***Cancer* 2000;89:1380–6.** © *2000 American Cancer Society.*

KEYWORDS: docetaxel, lymphopenia, $CD4^+$ lymphocytes, infections, solid tumors.

Infectious episodes are relatively frequent complications of cancer chemotherapy treatment, but most of these episodes complicate chemotherapy-induced neutropenia. However, infections also may develop in the absence of neutropenia, suggesting that additional, most probably immunologic mechanisms, may be involved in their pathogenesis. Indeed, immune dysfunction may be induced by anticancer agents, i.e., the well known fludarabine-induced $CD4^+$ lymphopenia, which may predispose to the development of opportunistic infections.[1–4]

Taxanes (paclitaxel and docetaxel) are new anticancer agents increasingly used in combination chemotherapy regimens for the treatment of malignant diseases. These drugs have a unique mecha-

nism of action promoting tubulin assembly in microtubules and inhibiting their depolymerization.[5,6] This results in stable, nonfunctional microtubule bundles, disrupting mitosis and, hence, cell division. In addition, in vitro exposure to low concentrations of paclitaxel induces severe nuclear envelope lesions (locally disrupted nuclear lamina, extensively clustered pore complexes, and disruption of resident proteins of the inner nuclear membrane) when the cells exit mitosis; then programmed cell death occurs 48–72 hours after cells are removed from paclitaxel-containing medium.[7]

Recently, it has been reported that patients with nonsmall cell lung carcinoma treated with weekly paclitaxel and irradiation presented an important $CD4^+$ lymphopenia that was frequently complicated with interstitial pneumonia.[8] An important $CD4^+$ and $CD8^+$ lymphopenia also was observed by our group in patients with nonsmall-cell lung carcinoma treated with weekly low doses of docetaxel (20–40 mg/m^2) in combination with irradiation; however, no opportunistic infections were observed during this trial.[9] Moreover, we recently reported that treatment of chemotherapy-naive breast carcinoma patients with the combination of docetaxel and mitoxantrone resulted in severe lymphopenia affecting all lymphocyte subsets.[10] Conversely, an unusually high incidence of nonneutropenic infections has been observed in patients with nonsmall cell lung carcinoma and advanced breast carcinoma treated with docetaxel-based regimens in the context of different Phase II trials conducted by our group.[11–15] The above data from the literature, as well as our own clinical experience from the administration of docetaxel-based regimens, led us to prospectively study the effect of docetaxel monotherapy on the immune system and, specifically, the quantitative alterations of the peripheral blood lymphocyte subsets.

PATIENTS AND METHODS

Patients

Forty-six chemotherapy-naive patients (median age, 65 years; range, 35–80 years) with histologically or cytologically confirmed nonsmall cell lung carcinoma (n = 10), breast carcinoma (n = 10), stomach carcinoma (n = 7), adenocarcinoma of pancreas and biliary tract (n = 11), endometrial carcinoma (n = 1), prostatic carcinoma (n = 1), ovarian carcinoma (n = 3), and central nervous system (CNS) gliomas (n = 3) entered the study. Twenty patients were males and 26 were females. The performance status (World Health Organization) was 0 in 17 (37%), 1 in 16 (35%), and 2 in 13 (28%) patients. In addition, 35 chemotherapy-naive patients with metastatic colorectal carcinoma treated with a combination of irinotecan (CPT-11) and continuous infusion of 5-fluourouracil (5-FU) and 20 previously untreated patients with CNS metastatic disease as the initial presentation of their cancer were enrolled as controls.

Treatment

Thirty-three patients were treated with docetaxel at a dose of 100 mg/m^2 over a 1-hour intravenous infusion every 3 weeks. Thirteen patients received docetaxel in a weekly schedule (35 mg/m^2/week, on Days 1, 8, and 15 every 4 weeks). All patients received appropriate premedication with 8 mg dexamethasone orally (p.o.) 12 and 4 hours before docetaxel administration and 4 mg p.o. twice daily for 3 additional days. No growth factors were administered prophylactically. Fifteen (45%), 9 (27%), and 9 (27%) of the 33 patients treated with docetaxel every 3 weeks received 2, 3 or 4, and $>$ 5 chemotherapy courses, respectively. Five (11%), 3 (7%), and 5 (11%) of the patients treated with the weekly schedule received 3, 2, and 1 cycles of chemotherapy, respectively. Patients with colorectal carcinoma received escalated doses of 5-FU (300–650 mg/m^2/day over a 24-hour continuous infusion for 4 consecutive days) and irinotecan (200–350 mg/m^2, over a 1-hour intravenous infusion on Day 4) every 3 weeks. Finally, patients with CNS metastatic disease were treated with 8 mg dexamethasone intravenously every 6 hours, for up to 7 days with concomitant mannitol and whole brain palliative irradiation.

Phenotypic Analysis of Peripheral Blood Lymphocytes

Peripheral blood samples for full blood count and immunophenotyping were drawn in Edathamil (EDTA)-containing tubes before and after the administration of chemotherapy, as follows: 1) in the group of patients treated with docetaxel every 3 weeks, i.e., on Days 0, 21, 42, and 63; 2) in the group of patients receiving weekly docetaxel every week before treatment; 3) in the group of patients with colorectal carcinoma on Days 0 and 64 (before the first and after the third cycle, respectively); and 4) in the group of patients with CNS metastatic disease on Day 0 before the initiation of dexamethasone treatment and on Day 7 of the treatment. All patients gave informed consent to participate in the study, which has been approved by the ethical and scientific committees of our institution. For immunophenotyping, 100 μL of the EDTA-containing blood was incubated with the appropriate volume of monoclonal antibody (moAb) for 15 minutes at room temperature. After the addition of 2 mL of red blood cell lysing solution (Immunoprep Kit; Coulter, Miami, FL), the samples were washed twice with phosphate-buffered saline (PBS)–containing azide (0.1% volume/volume [v/v]) and stored in PBS

containing paraformaldehyde (1% v/v). Cells were either analyzed immediately or stored at 4 °C overnight before analysis. The following moAbs were used: anti-CD3 (IOT3; pan-T cells), anti-CD4 (IOT4), anti-CD8 (IOT8), anti-CD20 (IOT20; a pan-B cells), and anti-CD56 (IOT 56; a natural killer [NK] cell–associated molecule). The moAbs were fluorescein isothiocyanate-labeled, and all were obtained from Immunotech (Lumigny, Marseilles, France). Irrelevant murine moAbs of the IgG1, IgG2a, and IgG2b subclasses were used to define background staining. Samples were analyzed by flow cytometry on a FACScan (Elite; Coulter) equipped with the Elite software 4.1. Lymphocytes were identified by forward- and side-scatter analyses; after daily calibration, a total of at least 10,000 cells were analyzed for each sample.

Statistical Analysis

Comparisons between patients and controls were performed by *t* tests for independent samples, whereas comparisons between pretreatment and posttreatment values for each lymphocyte subpopulation were performed using the Student *t* test for paired observations and the Fisher exact test. The weekly variability of lymphocyte subsets was analyzed by the analysis of variance for repeated measures,[16] and the degrees of freedom were adjusted by using the Greenhouse and Geisser correction factor.[17,18]

RESULTS

Immunophenotype of Peripheral Blood Lymphocytes

The absolute neutrophil and lymphocyte counts of 33 patients treated with docetaxel every 3 weeks were evaluated on Day 0 and 21 before the administration of the first and second cycle of chemotherapy, respectively. The absolute neutrophil count on Day 21 was not different from that on Day 0 (5451 ± 557 cells/dL and 5441 ± 783 cells/dL, respectively; $P = 0.157$). The absolute number of lymphocytes on Days 0 and 21 was 1200 ± 327 cells/dL and 830 ± 575 cells/dL, respectively ($P = 0.065$); however, 7 (21%) patients presented severe (< 500 cells/dL) lymphopenia on Day 21.

The phenotypic analysis of peripheral blood lymphocytes on Days 0 and 21 demonstrated that the absolute number of all the T-cell subsets ($CD3^+$, $CD4^+$, and $CD8^+$) and NK cells ($CD56^+$) but not of B cells ($CD20^+$) were significantly decreased after 1 course of docetaxel (Table 1). However, a significant decrease of the absolute number of $CD20^+$ cells also was observed after the administration of the second chemotherapy course (150 ± 134 cells/dL vs. 69 ± 83 cells/dL on Days 0 and 42, respectively; $P < 0.01$). Eighteen (55%) patients had < 400 $CD4^+$ cells/dL, 15 (45%) < 50 $CD20^+$ cells/dL, and 8 (24%) < 100 $CD56^+$ cells/dL by the end of the first chemotherapy course (Table 2). The administration of a second docetaxel course resulted in a further decrease of the absolute number of $CD3^+$, $CD4^+$, and $CD8^+$ but not of $CD56^+$ cells (not shown). Table 2 demonstrates that the number of patients with severe lymphopenia (< 500 cells/dL) or severe $CD4^+$, $CD20^+$, and $CD56^+$ lymphopenia could not be significantly increased after the administration of a second docetaxel dose.

To exclude the possibility that the observed lymphopenia was due to the corticosteroids, used as pre- and postmedication for docetaxel, we also analyzed the phenotype of peripheral blood lymphocytes from a group of chemotherapy-naive patients with CNS metastatic disease, treated with high doses of corticosteroids. The absolute number of lymphocyte subsets before and after the administration of dexamethasone is presented in Table 3; this 7-day high dose dexamethasone treatment induced a significant decrease

TABLE 1
Absolute Number of Peripheral Blood Lymphocyte Subsets after the First Docetaxel Course

	Absolute no./dL of cells (mean ± SD)		
Lymphocyte subset	Pretreatment (d = 0) (n = 33)	Posttreatment (d = 22) (n = 33)	*P* value
CD3	1136 ± 629	629 ± 449	< 0.005
CD4	629 ± 320	345 ± 250	< 0.01
CD8	443 ± 269	252 ± 190	< 0.01
CD20	150 ± 134	94 ± 119	NS
CD56	345 ± 215	195 ± 156	< 0.01
CD45RO	316 ± 221	181 ± 186	< 0.01

SD: standard deviation; NS: not significant.
The phenotype of peripheral blood lymphocyte subpopulations was evaluated from whole blood as described in "Patients and Methods."

TABLE 2
Incidence of $CD4^+$, $CD20^+$, and $CD56^+$ Lymphopenia during Docetaxel Administration Every 3 Weeks

	No. of patients (%)		
Dose	Pretreatment (n = 33)	First course (n = 33)	Second course (n = 30)
ALN < 500/dL	0 (0)	7 (21)	5 (17)
$CD4^+$ < 400/dL	7 (21)	18 (55)	15 (50)
$CD20^+$ < 50/dL	3 (9)	15 (45)	10 (33)
$CD56^+$ < 100/dL	3 (9)	8 (24)	8 (27)

ALN: absolute lymphocyte number.
The phenotype of peripheral blood lymphocyte subsets was determined as described in "Patients and Methods".

TABLE 3
Phenotype of Peripheral Blood Lymphocytes of Patients with CNS Metastatic Disease under Treatment with High Doses of Corticosteroids

	Absolute no./dL (mean ± SD)		
Lymphocyte subset	Before corticosteroids (n = 20)	After corticosteroids (n = 20)	*P* value
CD3	889 ± 479	680 ± 412	NS
CD4	488 ± 319	399 ± 283	NS
CD8	316 ± 184	235 ± 188	NS
CD20	161 ± 142	169 ± 157	NS
CD56	322 ± 170	203 ± 132	< 0.002

CNS: central nervous system; SD: standard deviation; NS: not significant.
Peripheral blood was obtained before and 7 days after the administration of high doses of corticosteroids. The phenotype of peripheral blood lymphocytes was determined as described in "Patients and Methods."

of $CD56^+$ cells (322 ± 170 cells/dL and 203 ± 132 cells/dL, respectively; $P = 0.002$), but not of the other lymphocyte subsets. Moreover, the administration of three courses of a nontaxane-based chemotherapy regimen (5-FU and irinotecan) had no effect on the absolute number of different lymphocyte subsets (Table 4), irrespectively of the studied dose level (not shown).

Quantitative Abnormalities of the Lymphocyte Subsets during the Weekly Docetaxel Administration and Their Recovery after Docetaxel Discontinuation

We previously have observed important quantitative phenotypic alternations in nonsmall cell lung carcinoma patients treated with weekly docetaxel in combination with radiotherapy.[9] To determine whether this phenomenon was due to docetaxel or to the combination of docetaxel and radiotherapy, we analyzed the phenotype of peripheral blood lymphocytes from 13 chemotherapy-naive patients who were treated with weekly docetaxel. As shown in Figure 1, the administration of the first weekly docetaxel dose resulted in a significant decrease of peripheral blood lymphocytes; moreover, the number of $CD3^+$, $CD4^+$, and $CD8^+$ but not of $CD20^+$ and $CD56^+$ was significantly decreased after the first administration of docetaxel. However, the administration of the second weekly docetaxel dose resulted in a significant decrease of the number of $CD20^+$ and $CD56^+$ but had no further effect on $CD3^+$, $CD4^+$, and $CD8^+$ cells.

The discontinuation of docetaxel treatment resulted in a significant increase of the absolute numbers of peripheral blood lymphocytes as well as of the $CD3^+$ and $CD4^+$ cells (Table 5); conversely, the absolute number of $CD8^+$, $CD20^+$, and $CD56^+$ cells remained low even after 1–3 months of treatment discontinuation.

Nonneutropenic Infectious Episodes during Docetaxel Treatment

Eight (17%) patients developed nonneutropenic infections during the 201 administered docetaxel courses. Only one of these patients presented a nonfebrile episode of Grade 4 neutropenia within the 30 days (Day 18), which preceded the development of the episode of nonneutropic infection. As shown in Table 6, five patients developed nonopportunistic infections (three patients presented a lower respiratory tract infection leading to respiratory insufficiency in two of them, a patient with a febrile urinary infection and a patient with gram-negative septicemia with unknown port of entry). All but 2 of these patients (Patients 8 and 24) had < 400 $CD4^+$ cells/dL; moreover, all but 1 patient (Patient 24) had < 50 $CD20^+$ cells/dL (Table 6). In addition, three patients developed opportunistic infections (two patients had herpes zoster and one generalized candidiasis) requiring hospitalization for specific treatment; all these patients also presented an extremely low absolute number of $CD4^+$ cells (< 100 $CD4^+$ cell/dL). All patients were uneventfully treated.

DISCUSSION

The results of the current study demonstrate that the administration of a single docetaxel dose in chemotherapy-naive patients resulted in severe lymphopenia concerning both T ($CD4^+$ and $CD8^+$) and NK ($CD56^+$) cells but not B ($CD20^+$) cells. This effect seems to be an early phenomenon because it was observed as early as 7 days after the administration of a low docetaxel dose; in addition, this observation strongly suggests that the lymphopenic effect of docetaxel may not be dose dependent. Moreover, further treatment with docetaxel also resulted in a significant B-cell lymphopenia. These observations clearly indicate that the docetaxel-associated lymphopenia is a generalized phenomenon and that it is not restricted to a specific lymphocyte subset. Indeed, 50%, 33%, and 27% of the patients treated with docetaxel every 3 weeks had < 400 $CD4^+$ cells/dL, 50 $CD20^+$ cells/dL, and 100 $CD56^+$ cells/dL, respectively, by the end of the second chemotherapy course (Table 2).

The effect of docetaxel on peripheral blood lymphocytes could not be attributed to the concomitant administration of corticosteroids because relatively higher doses of corticosteroids given for 7 days in a group of chemotherapy-naive patients with CNS metastatic disease resulted in a significant decrease of $CD56^+$ but not of $CD3^+$, $CD4^+$, $CD8^+$, or $CD20^+$ cells. In addition, treatment of chemotherapy-naive pa-

TABLE 4
Phenotype of Peripheral Blood Lymphocytes of Patients with Advanced Colorectal Carcinoma Treated with CPT-11 and 5-FU

	MTD[a] level (n = 5)			DLT[b] level (n = 3)		
Lymphocyte subset	Before treatment	After 3 cycles	*P* value	Before treatment	After 3 cycles	*P* value
$CD3^+$	921 ± 485[c]	847 ± 376	NS	1033 ± 638	1172 ± 281	NS
$CD4^+$	480 ± 224	484 ± 259	NS	538 ± 377	613 ± 289	NS
$CD8^+$	292 ± 186	251 ± 101	NS	349 ± 254	370 ± 184	NS
$CD20^+$	81 ± 43	76 ± 71	NS	99 ± 75	128 ± 42	NS
$CD56^+$	260 ± 153	242 ± 124	NS	347 ± 306	327 ± 128	NS

5-FU: 5-fluourouracil; MTD: maximum tolerated dose; DLT: dose-limiting toxicity; NS: not significant; SD: standard deviation.
[a] Defined at the 5-FU dose of 600 mg/m^2 continuous infusion for 4 days and CPT-11 at 350 mg/m^2 i.v. infusion on Day 1.
[b] Reached at the 5-FU and CPT-11 dose of 650 mg/m^2 for 4 days continuous infusion and 350 mg/m^2 i.v. infusion, respectively.
[c] Results represent the mean ± SD of the observed individual values of the absolute number of lymphocyte subset/dL.

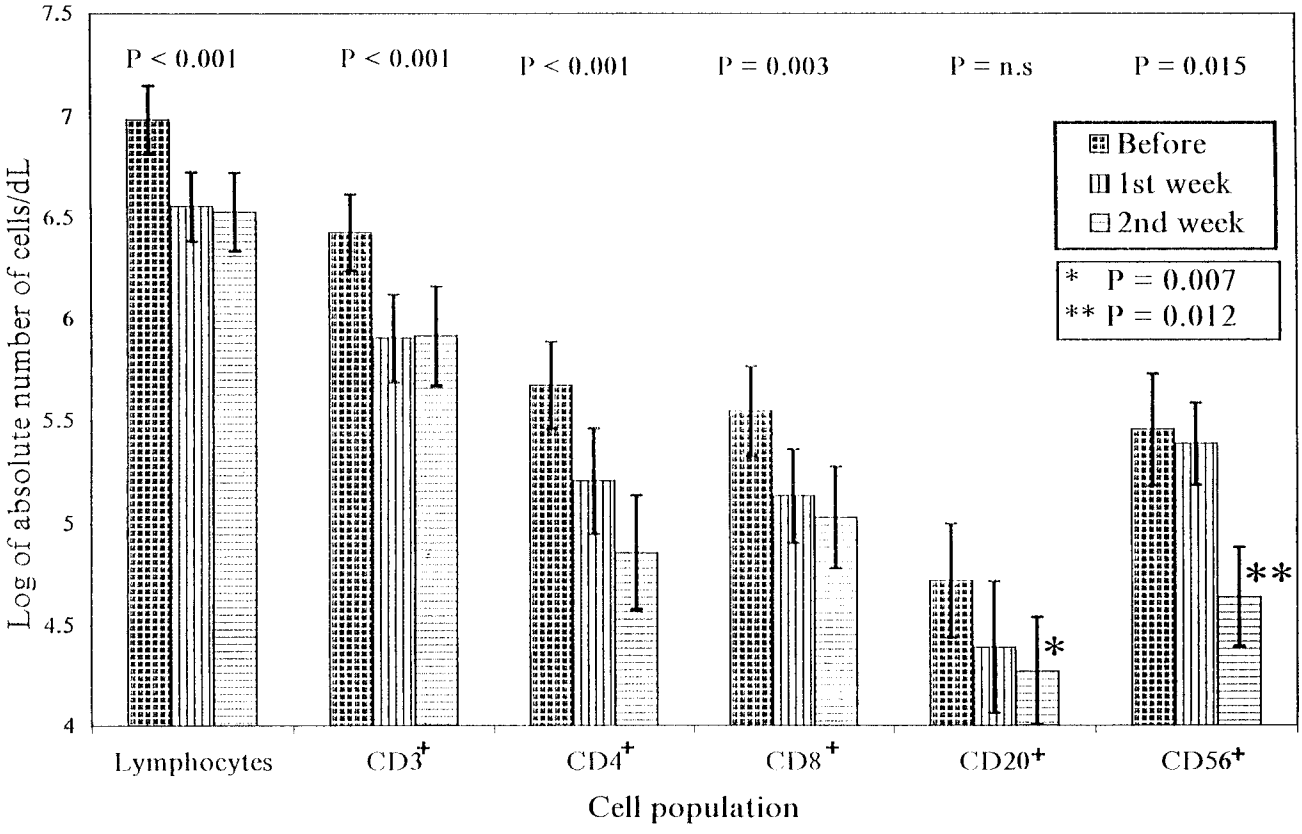

FIGURE 1. Changes in of the absolute number of lymphocytes and different peripheral blood lymphocyte subpopulations during the weekly administration of docetaxel are shown. The results are expressed on the mean ± standard deviation of the observed individuals values per deciliter.

tients with colorectal carcinoma with a different chemotherapy regimen combining 5-FU and irinotecan failed to produce any effect on the different peripheral blood lymphocyte subpopulations. Taken together, these observations strongly suggest that the lymphopenic effect of docetaxel is a drug specific phenomenon. Because low weekly doses of docetaxel also resulted in a similar significant decrease of the peripheral blood lymphocyte subpopulations, it is reasonable to hypothesize that the lymphopenia that was observed in the studies associating paclitaxel or docetaxel and irradiation[8,9] is due to the taxane itself and not to a combined effect of chemoirradiation. However, note that this lymphopenic effect of docetaxel on

TABLE 5
Modifications of Peripheral Blood Lymphocyte Subpopulations after Discontinuation of Docetaxel Treatment

	Absolute no. (cell/dL) (mean ± SD)		
Lymphocyte	During docetaxel treatment (n = 14)	1–3 mos after docetaxel discontinuation (n = 20)	*P* value
Total lymphocytes	1004 ± 604	1550 ± 590	< 0.003
$CD3^+$	617 ± 346	1148 ± 288	< 0.001
$CD4^+$	271 ± 165	560 ± 231	< 0.001
$CD8^+$	371 ± 277	474 ± 146	< 0.194
$CD20^+$	97 ± 131	171 ± 175	< 0.146
$CD56^+$	289 ± 288	391 ± 206	< 0.123

SD: standard deviation.
The phenotype of peripheral blood lymphocytes was determined as described in "Patients and Methods."

TABLE 6
Nonneutropenic Infections in Patients Treated with Docetaxel

		Absolute no. of cells/dL		
Patient no.	Infectious episode	$CD4^+$	$CD20^+$	$CD56^+$
7	Lower respiratory infection	294	45	160
8	Lower respiratory infection	542	41	153
10	Urinary infection	61	16	51
18	Reactivation of HZV infection	90	32	84
24	Lower respiratory infection	468	94	730
25	Generalized candidiasis	92	37	159
26	Gram-negative septicemia	309	19	ND
32	Reactivation of HZV infection	86	27	73

HZV: herpes zoster virus; ND: not determined.

peripheral blood lymphocytes is partially reversible because the absolute number of total peripheral blood lymphocytes, $CD3^+$, and $CD4^+$ but not of $CD8^+$, $CD20^+$, and $CD56^+$ cells had essentially returned to pretreatment values within 1–3 months after treatment discontinuation.

As described above, the pattern of docetaxel-mediated lymphocyte depletion is not restricted to a specific lymphocyte subset. A similar depletion of $CD4^+$ and $CD20^+$ lymphocytes also has been described for patients receiving intensive chemotherapy;[19–22] however, in this particular case an impaired regeneration of $CD4^+$ cells has been shown.[3,4,21–23] In contrast, in the case of the new purine analogs, the mechanism of $CD4^+$ lymphopenia has been attributed to the irreversible inhibition of adenosine deaminase resulting in an intracellular accumulation of deoxyadenosine and adenosine, thus leading to a severe acquired immunodeficiency syndrome.[24–27] The mechanisms that are responsible for the lymphopenic effect of docetaxel are not obvious. In vitro data have shown that brief exposure of Ishikawa endometrial adenocarcinoma cells to low concentrations (10 nM) of paclitaxel is associated with distinct nuclear envelope lesions at the exit from mitosis; more specifically, the cells present focally disrupted nuclear lamina and extensively clustered or incomplete pore complexes; these striking defects became evident 7–24 hours after the cells were removed from the drug-containing culture medium and could be readily discerned from normal-looking nuclei, lobulated nuclei, or micronuclei. These modifications lead to morphologic and biochemical evidence of programmed cell death 48–72 hours after the cells were removed from the paclitaxel-containing culture medium.[7] Although it is yet unclear whether cell exposure to docetaxel has a similar effect, that during the in vivo administration of docetaxel the peripheral blood lymphocytes are temporarily exposed to extremely higher drug concentrations than the 10 nM of paclitaxel, which lead to apoptosis. It will be of interest in a future study to compare the lymphopenic effect of docetaxel with that of paclitaxel, because the current study was clearly oriented to investigate the docetaxel-associated lymphopenia.

Eight (17%) patients in the current study developed nonneutropenic infections (5 nonopportunistic and 3 opportunistic) during the 201 docetaxel courses. Most of these patients had an extremely low absolute number of $CD4^+$ (< 400/dL) and $CD20^+$ (< 50/dL) cells. This observation suggests that patients treated with docetaxel may develop an impaired immune function and therefore develop clinically relevant infections. This corroborates with the frequency of nonneutropenic infections developing in patients treated with docetaxel-based regimens.[11–15] Recently, we observed that the incidence of nonneutropenic infections in cancer patients treated with docetaxel-based chemotherapy is by far higher than the nonneutropenic infections observed in our department with chemotherapy regimens that did not contain taxanes (G. Samonis, personal communication). Alternatively, taking into consideration the highly neutropenic effect of docetaxel, we cannot exclude that these nonneutropenic infections were initiated during a preceding period of profound neutropenia, due to docetaxel treatment and the infections were diagnosed when patients were no longer neutropenic. However, only 1 patient presented Grade 4 neutropenia within the 30 days that preceded the development of the nonneutropenic infection. Further studies are needed to elucidate this point.

In conclusion, the results of the current study demonstrate that docetaxel has a direct, probably cytotoxic, effect on peripheral blood lymphocytes that

may be associated with an increased risk for nonneutropenic infections. Additional studies are needed to evaluate the clinical relevance of this docetaxel-associated effect.

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