ABSTRACT

The in vivo cytokinetic effects on bone marrow cells from 19 patients with leukemia and lymphoma were investigated following a 5-day continuous i.v. infusion of ifosfamide (a congener of cyclophosphamide) at a daily dose of 1.0 to 1.8 g/sq m. There were 8 patients without bone marrow involvement by tumor cells at the time of study, and 11 patients had various degrees of neoplastic replacement. Ifosfamide induced a shift in DNA compartment distribution as determined by pulse cytophotometry, promoting a significant increase of cells in (G, + M) phase and a decrement of the G1,0 fraction. The mitotic index prior to and after ifosfamide administration seldom exceeded the corresponding (G, + M) compartment size, and the relative changes of DNA histogram-derived (G, + M) fractions and mitotic indices were consistent with a relative increase of cells in G, phase in 13 of 16 evaluable observations. Among the variables tested (ifosfamide dose, degree of marrow replacement by neoplastic cells, size of pretreatment S-phase compartment, percentage of myeloid and erythroid precursors), the percentage of nucleated red cells in the bone marrow prior to therapy was most closely related to the degree of ifosfamide-induced (G, + M) accumulation. This suggests that the kinetic changes primarily involve the erythroid precursor compartment. Absence of drug-induced anemia indicates a transient G, delay rather than an irreversible G2 block preceding cell death and/or preferential kill of G1,0 cells. In the subgroup of patients with more than 75% neoplastic cells in their bone marrow, S-phase increment was the predominant kinetic effect, which was not associated with clinical response.

INTRODUCTION

In addition to their cytotoxic effects, many chemotherapeutic agents have been shown to interfere with the progression of cells through the mitotic cycle (13). Such kinetic effects are detectable within the immediate life span of the proliferating target cells and are therefore early cellular events preceding the manifestation of lethal injury. Knowledge of the kinetic effects of antitumor compounds may be advantageously used for the design of chemotherapy trials, both for the selection of different drugs in combination chemotherapy programs and for the timing of their administration (33). With the introduction of automated flow-through systems, e.g., PCP (15, 17), and with the use of appropriate fluorochromes (9), measurement of intracellular compounds such as DNA can be rapidly performed. Since DNA content is a function of cell age (29, 34), determination of DNA distribution in a given cell population permits cell cycle analysis within minutes (6, 10, 15, 21). Thus, PCP complements the determination of the [3H]dThd LI, which measures the fraction of cells undergoing DNA synthesis (19), and of the MI, which is the percentage of cells in the various stages of mitosis, by yielding the percentage of distribution of cells in all phases of the cell cycle at 1 time. Sequential DNA histograms following administration of a chemotherapy agent provide information on drug-induced changes in compartment distribution (2, 16, 31, 35), which are the result of interference with cell progression in 1 or more cycle stages.

Ifosfamide is an analog of cyclophosphamide differing from the parent compound in that the 2 functional chloroethyl groups are not attached to the same nitrogen (8). Ifosfamide has demonstrated activity in acute leukemia, malignant lymphoma, lung carcinoma, and gastrointestinal and genitourinary carcinoma (7, 26, 28). Unlike other alkylating agents, myelosuppression is minimal and infrequent with ifosfamide (7). The dose-limiting toxicity is hemorrhagic cystitis, presumably related to active metabolites in the urine (7, 23, 28, 32). In an attempt to minimize bladder toxicity, at this institution ifosfamide has recently been given as a 5-day continuous infusion at a dose of 1200 to 1800 mg/sq m/day to 42 patients with leukemia and malignant lymphoma (27). This presented the unique opportunity to analyze the kinetic effects of this 5-day continuous infusion schedule of an alkylating agent on human neoplastic and normal marrow populations in vivo. Since other alkylating agents, such as Yoshi 864 (12), phenylalanine mustard (3), and peptic hemiofo in vitro (5) and cyclophosphamide in vivo (1), have shown cell cycle progression delay in G2 phase, this study was designed to determine whether ifosfamide exerts a similar kinetic effect on human neoplastic and normal cell populations in vivo. Sample heterogeneity and absence of antitumor effect from the analyzed courses of ifosfamide do not permit assessment of the relationship between effects on cycle progression and clinical response.

MATERIALS AND METHODS

Any patient with leukemia or malignant lymphoma (with or without bone marrow involvement) receiving ifosfamide

1 Supported in part by Grants CA-05831, CA-14528, and CA-11430 from the National Cancer Institute, NIH, Bethesda, Md. 20014.

2 The abbreviations used are: PCP, pulse cytophotometry; [3H]dThd, tritiated thymidine; LI, labeling index; MI, mitotic index.
as a 5-day continuous infusion (1.0 to 1.8 g/sq m/day) was eligible for this study. After informing each patient of the investigational nature of this treatment, written informed consent was obtained. There were 7 patients with non-Hodgkin’s lymphoma and 12 patients with leukemia (8 with acute lymphocytic or undifferentiated leukemia, 2 with acute myelogenous leukemia, and 2 with chronic lymphocytic leukemia). Bone marrow aspiration was performed just prior to and at the end of the 5-day infusion of ifosfamide. Bone marrow was aspirated from the posterior iliac crest. Morphological analysis and determination of MI were performed on routine bone marrow smears stained with May-Grünwald-Giemsa. After reinsertion of the Illinois needle at a different site, 1 to 2 ml of heparinized bone marrow were obtained for cytokinetic studies. This specimen was incubated with \[^{3}H\]dThd, 5 \(\mu\)Ci/ml (specific activity, 6.7 Ci/mmol), for 1 hr at 37°. After Hypaque-Ficoll sedimentation 1 aliquot of the interphase cells was processed for autoradiography (cytocentrifuge preparation); the remainder was fixed in 70% ethanol and stained with ethidium bromide, 12.5 \(\mu\)g/ml, and mithramycin, 25 \(\mu\)g/ml, for analysis of DNA distribution by PCP (6).

The MI was computed as percentage of mitotic figures among 3000 nucleated cells. The overall \[^{3}H\]dThd LI was computed as percentage of labeled cells per 1000 nucleated cells. The LI of neoplastic cells represents the percentage of labeled malignant cells among all malignant cells scored within a total of 1000 nucleated cells. Measurements of DNA distribution were routinely performed on 50,000 to 100,000 cells, and a computer model similar to that of Fried (22). The MI was computed as percentage of mitotic figures among 3000 nucleated cells. The overall \[^{3}H\]dThd LI was computed as percentage of labeled cells per 1000 nucleated cells. The LI of neoplastic cells represents the percentage of labeled malignant cells among all malignant cells scored within a total of 1000 nucleated cells. Measurements of DNA distribution were routinely performed on 50,000 to 100,000 cells, and a computer model similar to that of Fried was used for the decomposition of DNA histograms into \(G_{1}\), \(S\), and \((G_{2} + M)\) compartments (14, 20).

Since in this study we were concerned with chemotherapy-induced changes of kinetic parameters, the variation between measurements associated with sample processing should be known. Our laboratory has already reported such information for the \[^{3}H\]dThd LI determination (22). For measurements of cellular DNA distribution, the following variables were considered: (a) the influence of sample processing; and (b) instrument-related factors. Replicate measurements of fluorochromed bone marrow cells did not reveal significant differences in the number of cells recorded in the various channels of the multichannel analyzer of an ICP 11 pulse cytophotometer (Phywe Co., Göttingen, Germany) (6). In a separate study bone marrow samples were split in half immediately after aspiration, and 2 aliquots were then processed as indicated above. Since the variance of the \(G_{1}\), \(S\), and \((G_{2} + M)\) fractions varied directly with the proportion in each fraction, a logarithmic transformation (base 10) was used to stabilize the variance and facilitate the calculation of normal tolerance regions. Applying this conversion to replicate bone marrow samples from 14 patients, the S.D.’s of the differences of the logarithms (base 10) of proportions were 0.025 for \(G_{1}\), 0.205 for \(S\), and 0.113 for \((G_{2} + M)\). When transformed back to proportions, any ratio of successive observations (largest to smallest) exceeding 1.12 for \(G_{1}\), 2.5 for \(S\), and 1.68 for \((G_{2} + M)\) would be considered to be significantly different (\(p \leq 0.05\)) and not occurring due to replication error. None of the replicate samples were judged significantly different. This information then permits the determination of individual changes as a result of therapy.

RESULTS

Nineteen patients form the basis of this report. Their clinical, hematological, and cytokinetic characteristics are summarized in Table 1. Twelve patients had a diagnosis of leukemia, of whom 8 had acute lymphocytic or undifferentiated leukemia, 2 had acute myelogenous leukemia, and 2 presented with chronic lymphocytic leukemia. The groups of patients with non-Hodgkin’s lymphoma (7 patients) was comprised of 3 patients with diffuse histiocytic lymphoma and 4 patients with nodular poorly differentiated lymphocytic lymphoma. There were 8 patients without bone marrow involvement at the time of study, 3 of whom never had lymphoma cells documented in their bone marrow and 5 of whom had achieved complete remission on previous ifosfamide therapy. The 11 patients with neoplastic cells in their marrow at the time of kinetic study are listed in order of increasing percentages of malignant cells on marrow smears. Two patients (14 and 19) were studied twice, so that a total of 21 courses is available for analysis. With regard to clinical response, none of the courses of ifosfamide listed in Table 1 promoted remission status or even hematological improvement, defined as a >25% reduction of the malignant infiltrate, which is the product of bone marrow cellularity estimated on clot section \(\times\) the percentage of neoplastic cells identified on smears (18).

Cytokinetic analyses were not always performed during the first treatment course; 7 patients were studied during their first course, 3 during the second, 7 during the third, 3 during the fourth, and 1 during the fifth course of ifosfamide. The daily dose of ifosfamide varied from 1.0 to 1.8 g/sq m; the majority of patients received 1.2 g/sq m/day for 5 days (11 patients).

The most consistent change in the kinetic parameters investigated in this study consisted of a shift in compartment distribution of cellular DNA content. Chart 1 shows the original DNA histograms obtained prior to and at the end of the 5-day continuous infusion of ifosfamide at a dose of 1.5 g/sq m/day. When compared to replicate sample variability (see "Materials and Methods"), for both treatment courses a significant increase in the proportion of cells in the \((G_{2} + M)\) compartment at the expense of the \(G_{1}\) compartment was observed. Thus, during the third course of ifosfamide an increment of cells in \((G_{2} + M)\) from 6 to 19% (\(p < 0.001\)) was found, and during the fourth course an increase from 2 to 20% (\(p < 0.001\)) was found. The S-phase compartment did not change during the initial course, and there was a nonsignificant increase from 16 to 23% during the subsequent course. Similarly, there was no significant change of the overall LI during the initial course; the subsequent course was associated with a decrease of the overall LI from 20.5 to 14.2%.

With the replicate sample variability of kinetic parameters established in a separate control study (see "Materials and Methods"), the significance of ifosfamide-induced changes in DNA compartment distribution was analyzed (Table 1). With the exception of 3 treatment courses, there was a
### Table 1
Clinical, hematological, and cytokinetic characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Prior to ifosfamide</th>
<th>At time of study</th>
<th>Response to course of ifosfamide</th>
<th>Ifosfamide dose (g/sq m/day)</th>
<th>Sample time course No.</th>
<th>% neoplastic cells</th>
<th>% myeloid precursors</th>
<th>% rubricytes</th>
<th>LI (%)</th>
<th>DNA distribution</th>
<th>MI (%)</th>
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<td>1</td>
<td>DHL</td>
<td>-</td>
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<td>1.2</td>
<td>1</td>
<td>0 30</td>
<td>44</td>
<td>11.5</td>
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<td>1</td>
<td>0 29</td>
<td>34</td>
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<td>1</td>
<td>0 37</td>
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<td>20.3</td>
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<td>NA</td>
<td></td>
</tr>
<tr>
<td>4</td>
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<td>+</td>
<td>in CR</td>
<td>1.2</td>
<td>2</td>
<td>0 47</td>
<td>19</td>
<td>15.4</td>
<td>19.2</td>
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<tr>
<td>5</td>
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<td>in CR</td>
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<td>3</td>
<td>0 37</td>
<td>25</td>
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<td>3</td>
<td>0 10</td>
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<td>24.2</td>
<td>8.1</td>
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<td>3</td>
<td>0 49</td>
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<td>+ NR</td>
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<td>2</td>
<td>7 19</td>
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<td>+</td>
<td>+ NR</td>
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<td>1.5</td>
<td>3</td>
<td>42 25</td>
<td>23</td>
<td>19.5</td>
<td>32.0</td>
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<td>2.3</td>
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<tr>
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<td>+ NR</td>
<td>1.8</td>
<td>3</td>
<td>44 1</td>
<td>54</td>
<td>26.5</td>
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<td>30</td>
<td>9.5</td>
<td>1.5</td>
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<tr>
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<td>AUL</td>
<td>+</td>
<td>+ NR</td>
<td>1.5</td>
<td>3</td>
<td>57 3</td>
<td>36</td>
<td>19.3</td>
<td>21.6</td>
<td>21</td>
<td>25</td>
<td>2.2</td>
</tr>
<tr>
<td>15</td>
<td>NPDL</td>
<td>+</td>
<td>+ NR</td>
<td>1.0</td>
<td>1</td>
<td>60 10</td>
<td>7</td>
<td>4.3</td>
<td>4.6</td>
<td>4</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>16</td>
<td>AML</td>
<td>+</td>
<td>+ NR</td>
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<td>30</td>
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<tr>
<td>17</td>
<td>CLL</td>
<td>+</td>
<td>+ NR</td>
<td>1.2</td>
<td>1</td>
<td>87 2</td>
<td>9</td>
<td>0.9</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
<td>0.9</td>
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<tr>
<td>18</td>
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<td>+</td>
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<td>1.8</td>
<td>5</td>
<td>88 2</td>
<td>9</td>
<td>2.8</td>
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<td>7</td>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td>19</td>
<td>ALL</td>
<td>+</td>
<td>+ NR</td>
<td>1.2</td>
<td>1</td>
<td>92 2</td>
<td>2</td>
<td>1.7</td>
<td>0.5</td>
<td>2</td>
<td>0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**a** DHL, diffuse histiocytic lymphoma; CR, complete remission; NA, not applicable; NPDL, nodular poorly differentiated lymphocytic lymphoma; AUL, acute undifferentiated leukemia; NE, not evaluable; ALL, acute lymphocytic leukemia; NR, no response; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia.

**b** The pre- to posttreatment difference is significant at ρ = 0.01.

**c** The pre- to posttreatment difference is significant at ρ = 0.05.

**d** (G_2 + M) compartment contains both normal diploid (G_2 + M) and neoplastic tetraploid G_1/0 cells; no appreciable tetraploid S and (G_2 + M) proportions were noted.
significant change in the proportion of cells in (G₂ + M) in the remainder of cases (p = 0.01 for 17 courses; p = 0.05 for 1 course), with a (G₂ + M) increment in 15 observations. The significant (G₂ + M) compartment change was frequently associated with a similarly significant decrease of cells in G₁₀ phase. In fact, there were 2 instances of nonsignificant (G₂ + M) increment for which the proportion of G₁₀ cells decreased significantly. Thus, in 20 of 21 treatment courses ifosfamide produced significant DNA compartment shifts involving either both (G₂ + M) and G₁₀ compartments or the latter alone.

Table 2 provides descriptive statistics on DNA compartment distribution prior to and at the end of ifosfamide infusion for all patients. Combining all treatment courses and with a log (base 10) transformation (see "Materials and Methods"), a significant increase in the proportion of cells in the (G₂ + M) compartment (p = 0.006) at the expense of the G₁₀ compartment (p = 0.019) was observed (paired t test). S-phase compartment size and LI did not change significantly.

Patients were then grouped by the extent of marrow involvement by neoplastic cells. Patients with <5% malignant cells were designated "normal"; patients with >5 and <75% neoplastic cells were considered as the "mixed" group; a third group of patients all had more than 75% neoplastic cells in their marrow, and this group was designated "leukemic". The normal group of 8 patients showed a significant compartment shift of cells out of G₁₀ and S into (G₂ + M) phase (p = 0.001). Patients with mixed marrow populations displayed a less pronounced and nonsignificant compartment shift out of G₁₀ into (G₂ + M) during ifosfamide administration. In the leukemic group there was a significant increase in the S-phase compartment (p = 0.028) at the expense of both G₁₀ and (G₂ + M). Both the pretreatment S-phase compartment and the pre- and posttreatment overall LI in the leukemic group were significantly lower (p < 0.002) than the corresponding values in the normal and mixed groups, which were not significantly different.

Chart 2 demonstrates the distribution of post-versus pre-

<table>
<thead>
<tr>
<th>DNA compartment changes associated with ifosfamide treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>All courses</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>G₁₀</td>
</tr>
<tr>
<td>Pretreatment</td>
</tr>
<tr>
<td>Posttreatment</td>
</tr>
<tr>
<td>S</td>
</tr>
<tr>
<td>Posttreatment</td>
</tr>
<tr>
<td>(G₂ + M)</td>
</tr>
<tr>
<td>Posttreatment</td>
</tr>
</tbody>
</table>

<sup>a</sup> Bone marrow with <5% tumor cells.
<sup>b</sup> Bone marrow with >5% and <75% tumor cells.
<sup>c</sup> Bone marrow with >75% tumor cells.
<sup>d</sup> Significant difference between compartment sizes pre- and posttreatment (details in text).
In Vivo Cell Kinetics of Ifosfamide

Chart 3. Correlation of [3H]dThd LI and S-phase fraction prior to therapy (A) and at the end of a 5-day continuous infusion of ifosfamide (B). Independent of the degree of bone marrow involvement by neoplastic cells (○, <5% tumor cells; •, >5% and <75% tumor cells; △, >75% tumor cells), there is a linear correlation between the overall [3H]dThd LI and the DNA histogram-derived percentage of cells in S phase both prior to (r = 0.783) and following ifosfamide therapy (r = 0.704).

Chart 4. Relationship between change of \((G_2 + M)\) compartment and Ml. The positive values indicate an increase and the negative numbers indicate a decrease of \((G_2 + M)\) compartment and Ml, respectively. Among 16 evaluable treatment courses, in 13 the Ml increased either to the same or to a lesser extent than did the \((G_2 + M)\) fraction, or the Ml decreased to the same or a greater extent than the proportion of \((G_2 + M)\) cells.

Chart 5. Magnitude of \((G_2 + M)\) change as a function of the percentage of nucleated RBC. Independent from the degree of marrow replacement by tumor cells (○, <5% tumor cells; •, >5% and <75% tumor cells; △, >75% neoplastic cells), there was a linear correlation between the \((G_2 + M)\) ratio posttreatment \((post Rx)\) versus prior to therapy \((pre Rx)\) and the percentage of rubricytes.
treatment fraction of cells in S phase did not determine the extent of \((G_2 + M)\) accumulation (Chart 7).

DISCUSSION

We have demonstrated that ifosfamide perturbs the cycle progression of bone marrow cells from patients with leukemia and lymphoma. For the entire group of patients with varying degrees of bone marrow replacement by neoplastic cells, a significant increase of the \((G_2 + M)\) compartment at the expense of cells in \(G_{1}\) phase was noted. Under the staining conditions used in this study, \(G_2\) and mitotic cells could not be distinguished (11). Since the MI did not change significantly, the \((G_2 + M)\) increment can be interpreted primarily as a delay of cells in the \(G_2\) traverse.

Another interpretation of the DNA distribution changes would be a preferential lethal damage of \(G_{1}\) cells. The available kinetic data do not permit a distinction between these 2 alternatives. Analysis of the hematological data indicated that the extent of DNA compartment shift into \(G_2\) was correlated with the pretreatment percentage of nucleated red cells. This would suggest that the kinetic changes primarily involved the erythroid precursor compartment. In a more extensive Phase 1 trial reported by Rodriguez et al. (26), there was no significant anemia associated with ifosfamide therapy. Therefore, it is unlikely that the observed DNA compartment shifts reflect preferential red cell precursor kill in \(G_{1}\) phase. Our kinetic data are consistent with a transient rather than an irreversible \(G_2\) block preceding cell death. Lack of correlation between the pretreatment S-phase percentage and the percentage of increase of the \((G_2 + M)\) proportion implies that S-phase cells were not the exclusive target cells for the induction of \(G_2\) delay by ifosfamide.

Cycle progression delay in \(G_2\) phase has been reported to be the major kinetic effect produced by a variety of antituumor compounds that we and others have investigated in vivo and in vitro (4, 25, 30). In particular, 3 alkylating agents [Yoshi 864, melphalan, and peptichemio (3, 5, 13)] were found to interfere with cycle progression of a human lymphoid cell line primarily in \(G_2\) phase. Cyclophosphamide, the parent compound of ifosfamide, has been demonstrated by Alberts and van Daalen Wetters (1) to accumulate cells in \(G_2\) phase.

A comparison between DNA histogram-derived S-phase fraction and \([^{3}H]\)dTd LI did not reveal a major discrepancy between these 2 parameters as a result of ifosfamide therapy (Chart 3). This implies that ifosfamide does not totally suppress DNA synthesis, nor do we have an indication for a significant delay in S-phase traverse for the whole population. In the overtly leukemic group of patients, ifosfamide treatment induced a significant increase of the low pretreatment proportion of cells in S phase, while there were varying changes in \((G_2 + M)\) compartment size for the individual patients. In view of the lack of clinical response in these patients, our kinetic observations of an S-phase increment are reminiscent of findings by Murphy et al. (24) reporting on the predictive value of a decrease in tumor cell LI in patients with solid tumors. In our study there were altogether 5 patients demonstrating a significant decrease in tumor cell LI without associated antitumor effect.

The absence of antitumor effect from the analyzed courses of ifosfamide in this study does not permit the relationship between \(G_2\)-phase delay as the major effect on cycle progression and clinical response to be analyzed. In the future it will be important to study the kinetic effects of new agents on neoplastic cells during their initial administration to test whether early detectable cycle perturbation effects may predict for clinical response, \(i.e.,\) lethal cell damage, to the agent under investigation.

REFERENCES

In Vivo Cell Kinetics of Ifosfamide


In Vivo Perturbation of Human Marrow Cell Cycle Progression by Ifosfamide


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