Table 3. Non-hematologic toxicity*

	I	II	III	IV
Infection	0	0	3	1
Cardiac	0	0	2	0
Neurologic (headache)	2	3	1	0
Stomatitis	0	0	1	0
Nausea	5	2	1	0
Vomiting	2	2	0	0
Elevated LFTs	6	3	0	1
BP/BP	1/2	0/0	0/0	0/0
Fatigue	1	1	1	0
Diarrhea	1	0	1	0
G.U.	2	0	0	0

*NCI common toxicity criteria; n=30.

grams), and so the precipitating factor is uncertain. This patient received another cycle of amonafide without complication.

The other cardiac event occurred after cycle 5 of amonafide in a patient with no previous cardiac history. The patient developed hypotension. The electrocardiogram revealed new T wave inversions in all leads. The nuclear ejection fraction was normal at 74% and the cardiac enzymes were normal. The echocardiogram revealed a very small pericardial effusion, an atrial septal aneurysm and normal wall motion. The patient received no further treatment with amonafide. As there was no other obvious precipitating factor, this event may have been drug-related.

Headache occurred in 20% (6 patients) of those entered: grade I or II (mild to moderate and transient) in 5 patients and as grade III (severe and unrelenting) in the sixth patient. The grade I/II headaches were generally brief and relieved with analgesics, however, one patient did have grade II headaches intermittently for one month following treatment. The one patient with a grade III headache developed it just prior to administration of the fifth dose in cycle 5. The headache lasted 5 days. A head CT revealed only mastoiditis. No further chemotherapy was given as the patient progressed and developed cardiac toxicity as described above.

Only one patient developed grade III nausea. Stomatitis occurred in only one patient during a period of grade IV leukopenia and thrombocytopenia.

Transient elevation of liver function tests occurred in 9 patients and consisted mostly of mild transaminase elevations. One patient developed grade II transaminase elevations transiently 2 weeks after therapy and then a brief grade IV elevation of bilirubin one month after treatment. Sonogram of the liver revealed only fatty changes.

Pharmacokinetic results

Using caffeine as a substrate, it has previously been demonstrated that the ratio of urinary concentration of two metabolites of caffeine 5-acetylamino-6-amino-3-methyluracil (AAMU) and 1-methylxanthine (1X) is a useful discriminator of acetylator phenotype [14].

Acetylator phenotyping was available in 21 of the 30 patients on the study. AAMU/1X ratios ranged from 0.03 to 11.6 with a median of 1.31 and a 75th percentile of 1.76. A molar ratio of AAMU/1X of 1.8 was used to distinguish fast and slow acetylators [16] (see Fig. 2). By this criterion, 4 of the 21 patients (19%, 90% confidence interval 7%–38%) were characterized as fast acetylators. Leukocyte nadirs were available for 18/21 patients for whom acetylator phenotyping was available, including 15 of the 17 slow acetylators and 3 of the 4 fast acetylators. In contrast to previous reports [12,15], there was no significant difference in the degree of leukocyte toxicity, ($p = 0.84$) (see Fig. 3). The fast acetylators contributed to one of the grade I toxicities and two of the grade II toxicities. The slow acetylators accounted for 1 grade I, 3 grade II and 4 grade IV toxicities. The absolute numbers of the grade I and II toxicities were nearly identical for the slow and fast acetylators, but all of the very toxic events occurred in slow acetylators. The two most severely affected patients with grade IV leukopenia and grade II or III thrombocytopenia were in fact the slowest acetylators in the group. The patient who tolerated the highest dose escalation, however (10% per cycle for 4 cycles), was a slow acetylator.

There was no association of the nadir leukocyte count with sex ($p = 0.45$) or race ($p = 0.77$). There was no association between the logarithm of either the pretreatment leukocyte count or the nadir leukocyte count and acetylator phenotype, race or sex. Upon further analysis, it was noted that patients at or above the median age of 59 years had a lower nadir leukocyte count than those younger than age 59 ($2.0/mm^3$ vs $7.1/mm^3$, $p = 0.05$).

There were no factors identified which were associated with the logarithm of nadir absolute neutrophil count. However, this finding is based on available data from only 15 patients. There was a suggestion of there being lower nadir absolute neutrophil counts for non-whites than those of whites, although this did not achieve statistical significance.