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Short report

Incidence of thrombocytopenia with gemcitabine-based therapy and influence of dosing and schedule

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Introduction

Thrombocytopenia is a common toxicity noted with anti-cancer therapies, including gemcitabine-based chemotherapy. A detailed analysis of thrombocytopenia resulting from gemcitabine-based therapy and its clinical implications has not been performed. This retrospective analysis was undertaken to evaluate thrombocytopenia associated with gemcitabine-based therapy. The primary objectives of this analysis were to determine the incidence of thrombocytopenia with gemcitabine-based therapy and to understand the clinical complications, such as hemorrhage, associated with thrombocytopenia. We also evaluated the impact of schedule (21- versus 28-day cycle) and cisplatin dose (100 versus $\leqslant 75$ mg/m^2) on the incidence of thrombocytopenia.

Patients and methods

We identified all gemcitabine-based phase II and III trials from the global Eli Lilly and Company database. We then identified all patients with grade 3/4 thrombocytopenia, as defined by WHO or Common Toxicity Criteria (CTC) grades ($<50\,000$/mm^3), reported in these trials. Of these patients, patients with grade 3 or 4 hemorrhage and those who received platelet transfusions were identified. Descriptive statistics were provided. Chi-square tests were also performed to understand the influence of dose and schedule.

The data analyzed in this report was compiled from the global Eli Lilly and Company database.

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Results

A total of 92 phase II and III gemcitabine-based trials were identified, of which 61 used single-agent gemcitabine (2609 patients) and 31 used gemcitabine-based combinations (1804 patients). Of the 177 patients who had grade 3 or 4 thrombocytopenia in the single-agent gemcitabine studies, only one had grade 3 or 4 hemorrhage (grade 4), although this patient did not require platelet transfusion. Of the 726 patients who had grade 3 or 4 thrombocytopenia among the studies using gemcitabine-containing regimens, only 10 had grade 3 or 4 hemorrhage (nine grade 3; one grade 4), five of whom required platelet transfusions. These results, as well as the results of a comparison of 21- versus 28-day schedules overall and by cisplatin dose, are summarized in Table 1.

Of the 1804 patients who received gemcitabine-based combinations, 1518 were on a 28-day schedule, 278 were on a 21-day schedule and eight were on a 42-day schedule. Of the patients on the 28-day schedule, 43% (648 of 1518) had grade 3 or 4 thrombocytopenia, compared to only 28% (78 of 278) of the patients on the 21-day schedule ($p<0.001$).

A total of 1705 (of the 1804) patients were treated with gemcitabine and cisplatin combinations. Of these patients, 1441 received <75 or 100 mg/m^2 cisplatin per cycle. With the lower cisplatin doses, a higher percentage of grade 3 or 4 thrombocytopenia was reported among patients on the 28-day schedule compared with that of patients on the 21-day schedule

Table 1. Rates of thrombocytopenia, hemorrhage and platelet transfusions with gemcitabine, on 28- versus 21-day schedules, and by cisplatin dose

Gemcitabine-based phase II and III Lilly sponsored trials (*n*=4413 patients)		
	Single-agent gemcitabine (*n*=2 609)	Gemcitabine combinations (*n*=1 804)
Grade 3/4 thrombocytopenia	177 (6.8%)	726 (40.2%)
Grade 3/4 hemorrhage	1 (0.6%)	10 (1.4%)
Platelet transfusions	35 (19.8%)	111 (15.3%)
Grade 3/4 hemorrhage and platelet transfusions	0	5 (0.7%)
All gemcitabine-based combination regimens (*n*=1804 patients)		
	28-day schedules (*n*=1 518)	21-day schedules (*n*=278)
Grade 3/4 thrombocytopenia[a]	648 (42.7%)	78 (28.1%)
All gemcitabine plus cisplatin combinations (*n*=1441 patients)[b]		
	Cisplatin $\leqslant$ 75 mg/m^{2}[c] (*n*=617)	Cisplatin=100 mg/m^{2}[d] (*n*=824)
Grade 3/4 thrombocytopenia	285 (46.2%)	389 (47.2%)
28-day schedule	*n*=531	*n*=718
	259 (48.8%)	345 (48.1%)
21-day schedule	*n*=86	*n*=106
	26 (30.2%)	44 (41.5%)

[a] $P<0.001$, based on a χ^2 test for the difference between schedules.
[b] An additional 264 patients had received different schedules and doses of cisplatin, and therefore could not be included in the analysis.
[c] $P=0.001$, based on a χ^2 test for the difference between schedules of the 75 mg/m^2 cisplatin dose.
[d] $P=0.204$, based on a χ^2 test for the difference between schedules of the 100 mg/m^2 cisplatin dose.

(49 [259/531] versus 30% [26/86]; $p=0.001$). With the higher cisplatin dose, however, the difference between the 28- and 21-day schedules in grade 3 or 4 thrombocytopenia rates was not significant (48 [345/718] versus 42% [44/106]; $p=0.204$).

This analysis could not be performed on the group of patients who received other gemcitabine-based combinations because of the small numbers of patients (etoposide=13, epirubicin=23, vinorelbine=2, carboplatin=14, ifosfamide=28, doxorubicin=11 and vinblastine=8).

Discussion

Gemcitabine-based combinations are associated with more thrombocytopenia than single-agent gemcitabine (40 versus 7%). However, clinical complications such as grades 3 and 4 hemorrhage are uncommon. A 21-day schedule is associated with less thrombocytopenia than a 28-day schedule. Cisplatin doses of 75 mg/m^2 or less produce less grades 3 and 4 thrombocytopenia with a 21-day schedule than a 28-day schedule, although the effect of schedule is lost when the dose of 100 mg/m^2 is used. Our evaluation of the need for platelet transfusions for patients with thrombocytopenia remains incomplete because patients did receive prophylactic transfusions, thus confounding the analysis.

Higher doses of cisplatin are known to cause more thrombocytopenia,[1,2] which might explain the higher incidence of thrombocytopenia seen with the higher cisplatin dose in the 21-day regimen with gemcitabine. Conte and colleagues[1] reported grades 3 and 4 thrombocytopenia in 13% of patients given a 100 mg/m^2 cisplatin dose versus 0% of patients given a 50 mg/m^2 dose in combination with fixed doses of cyclophosphamide and epidoxorubicin. Gandara *et al.*[2] showed that increasing the cisplatin dose from 50 to 100 mg/m^2 (both given on days 1 and 8, every 28 days) increased grade 3 or 4 thrombocytopenia from 2 to 15%, respectively. However, the additional dose of gemcitabine may result in a higher incidence of thrombocytopenia because the 28-day cycle produced more thrombocytopenia than the 21-day cycle, regardless of the cisplatin dose. It should be noted that the higher dose of cisplatin seems to have a greater effect than the additional dose of gemcitabine (Table 1).

Conclusion

In conclusion, gemcitabine monotherapy produces less thrombocytopenia than gemcitabine combinations, but the thrombocytopenia is infrequently associated with hemorrhage. Dose and schedule do influence the incidence of thrombocytopenia. A 21-day schedule employing cisplatin doses <100 mg/m^2 is associated with less thrombocytopenia.

References

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