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The Effect of Lithium Carbonate on Chemotherapy-Induced Neutropenia and Thrombocytopenia

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Lithium carbonate ameliorates neutropenia associated with cancer chemotherapy. The effect of lithium on platelet suppression has not, however, been well established. In the present study, five patients with ovarian carcinoma received daily lithium during alternate cycles of treatment with hexamethylmelamine, cyclophosphamide, adriamycin, and cis-platinum. Analysis of myelosuppression was performed on 24 paired consecutive cycles given at identical doses, one with and one without lithium. During lithium cycles, nadir leukocyte, neutrophil, and platelet counts were significantly higher ($P<0.01, <0.01, <0.05$ respectively) and the interval between treatments was shorter ($P<0.01$). One patient who has received 11 cycles of chemotherapy continues to receive 100% doses owing to the beneficial effect of lithium on chemotherapy-induced thrombocytopenia. Lithium was poorly tolerated by some patients because of either tremor or nausea and vomiting, in spite of nontoxic serum lithium levels. The amelioration of drug-induced platelet suppression as well as neutrophil suppression noted in this study suggests that lithium's effect on hematopoiesis is not limited to stimulation of neutrophil production. The ability of lithium to decrease chemotherapy-induced myelosuppression suggests that lithium administration may facilitate escalation of chemotherapy doses in selected patients.

Key words: lithium, chemotherapy-induced myelosuppression, CFU-C, colony-stimulating activity

INTRODUCTION

Lithium carbonate, a drug used to treat manic-depressive disease, induces a neutrophilic leukocytosis in psychiatric patients [1–4]. Lithium therapy improves neutrophil counts in patients with Felty syndrome [5] and in some congenital and acquired forms of neutropenia [5–9], and ameliorates chemotherapy-induced neutropenia in patients with solid tumors and leukemia [10–18]. None of the studies using lithium in conjunction with chemotherapy has shown a significant effect of lithium on

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platelet counts, although Bille et al. [4] reported an elevation of platelet counts in psychiatric patients taking lithium. Animal studies suggest that lithium may have an effect on the pluripotential hematopoietic stem cell, as well as its established effect of increasing granulocyte production by stimulating formation of colony-stimulating activity (CSA), the regulatory protein required for in vitro (and perhaps in vivo) proliferation and differentiation of neutrophil precursors [19–26].

The present study was undertaken to determine whether lithium could attenuate the platelet depression associated with a chemotherapy regimen which characteristically produces cumulative marrow toxicity, particularly thrombocytopenia. Patients with ovarian carcinoma received lithium during alternate cycles of chemotherapy. In a paired comparison of 24 cycles given at identical doses of cytotoxic agents, lithium significantly ameliorated thrombocytopenia as well as neutropenia.

MATERIALS AND METHODS

Patient Population

Consecutive patients with advanced (stage III or IV) or recurrent epithelial ovarian carcinoma receiving combination chemotherapy who were not on diuretics or sodium-restricted diets were asked to participate in the lithium study. Eight patients agreed and gave written informed consent. Three of these patients could not tolerate lithium because of severe nausea and vomiting (with nontoxic lithium levels) and withdrew from the study after less than 2 weeks. The remaining five patients received lithium on alternate cycles of chemotherapy. These patients ranged in age from 48 to 61 years (median 60). Four had stage III tumor and had received no prior chemotherapy. One patient had recurrent disease after 13 courses of melphalan chemotherapy. During the study, the five patients completed from one to seven cycles of chemotherapy on lithium (median, 5 cycles) and from two to six cycles off lithium (median, 5 cycles).

Chemotherapy

Patients received hexamethylmelamine 150mg/m^2 orally for 7 days, cyclophosphamide 600 mg/m^2, adriamycin 30 mg/m^2, and cis-platinum 50 mg/m^2 intravenously every 3–4 weeks. One patient previously treated with melphalan received 5-fluorouracil 600 mg/m^2 instead of cyclophosphamide. Doses of hexamethylmelamine, cyclophosphamide, adriamycin, and 5FU were adjusted based on the blood counts on the day of treatment. Seventy-five percent doses were given if the WBC was less than 4,000/mm^3 and the platelets $\geqq$ 150,000/mm^2; 50% doses were given if the WBC was less than 3,500/mm^3 and/or the platelets less than 150,000/mm^3. Therapy with myelosuppressive drugs was withheld if the WBC was less than 2,500/mm^3 and/or the platelets less than 100,000/mm^3.

Lithium Treatment

Patients received lithium carbonate on alternate cycles of chemotherapy at an initial dose of 300 mg three times daily. Lithium dosage was modified on the basis of weekly serum lithium levels and the levels were maintained at 0.6 to 1.3 meq/liter. Lithium was begun on day 2 of the chemotherapy cycle and continued until the day prior to the next chemotherapy treatment.

Blood Counts

Weekly white blood counts, hemoglobin, hematocrit, and platelet counts were performed using a Coulter model S+. Differential counts were generally done by a Hematrek automated differential counter (Geometric Data, Wayne, PA). Some differentials were performed manually. In both cases, 100 cells were counted to determine the differential. Absolute neutrophil counts included polymorphonuclear and band forms (Tables I, II).

TABLE I. Effect of Lithium on Myelosuppression for Paired Consecutive Cycles of Chemotherapy Given at the Same Dose

		Blood counts ($\times 10^3/mm^3$)[a]		
Cell type		On lithium	Off lithium	
Total leukocytes:	Nadir	3.2 ± 0.3	2.4 ± 0.2	$P < 0.01$[d]
	Δ-nadir[b]	−1.5 ± 0.3	−3.2 ± 0.5	$P < 0.001$
	Δ/cycle[c]	0.5 ± 0.4	−1.6 ± 0.4	$P < 0.01$
Neutrophils:	Nadir	1.8 ± 0.3	1.0 ± 0.2	$P < 0.01$
	Δ-nadir	−1.2 ± 0.4	−2.6 ± 0.4	$P < 0.01$
	Δ/cycle	0.4 ± 0.4	−1.5 ± 0.4	$P < 0.01$
Platelets:	Nadir	159 ± 14	124 ± 22	$P < 0.05$
	Δ-nadir	−116 ± 28	−90 ± 27	NS
	Δ/cycle	−39 ± 17	−30 ± 40	NS

[a]Mean ± SEM for 12 cycles on lithium and 12 cycles off lithium.
[b]Blood count on day 1 of cycle minus lowest blood count in that cycle.
[c]Blood count on day 1 of cycle minus blood count on day 22.
[d]Statistical significance using paired t-test.
NS = not significant.

TABLE II. Effect of Lithium on Myelosuppression During Chemotherapy

		Blood counts[a]		
Cell type		All cycles on lithium	All cycles off lithium	
Total leukocytes:	Nadir	2.9 ± 0.2	2.6 ± 0.2	NS
	Δ-nadir[b]	−1.7 ± 0.3	−2.8 ± 0.4	$P < 0.05$[d]
	Δ/cycle[c]	0.1 ± 0.4	−1.1 ± 0.3	$P < 0.02$
Neutrophils:	Nadir	1.7 ± 0.3	1.3 ± 0.2	NS
	Δ-nadir	−1.4 ± 0.3	−2.3 ± 0.4	$P = 0.02$
	Δ/cycle	0.1 ± 0.3	−1.1 ± 0.3	$P < 0.02$
Monocytes:	Peak value	0.5 ± 0.1	0.4 ± 0.0	NS
Platelets:	Nadir	158 ± 12	156 ± 31	NS
	Δ-nadir	−150 ± 29	−107 ± 71	NS
	Δ/cycle	−43 ± 16	−41 ± 26	NS
Red cells—hematocrit	Δ/cycle	−2.7 ± 3.2	−2.4 ± 4.2	NS

[a]Mean ± SEM for 19 cycles on lithium and 21 cycles off lithium. For leukocytes, neutrophils, monocytes, and platelets, values are $\times 10^3/mm^3$; for hematocrits, values are percents.
[b]Blood count on day 1 of cycle minus lowest blood count in that cycle.
[c]Blood count on day 1 of cycle minus blood count on day 22.
[d]Statistical significance using two-tailed Student's t-test.
NS = not significant.

CFU-C Assay

Heparinized blood samples were obtained prior to the initiation of chemotherapy and prior to each course of chemotherapy. In some cases, samples were obtained weekly. Mononuclear cells were obtained by ficoll-hypaque density-gradient separation and were plated in a methylcellulose culture system [27–29]. CSA was obtained from the supernatant of 7-day cultures of normal peripheral blood mononuclear cells incubated at a concentration of 10^6 cells/ml in 20% fetal calf serum and alpha medium (Flow Laboratories, Rockvillle, MD) in the presence of 1% phytohemagglutinin (PHA, Wellcome Research Laboratories, Beckenham, England) [24,30]. Dose-response curves were performed for each batch of standard CSA using normal bone marrow mononuclear cells to assure maximal colony stimulation. Quadruplicate culture plates containing 2×10^5 patient peripheral blood monocuclear cells/ml were incubated at 37°C in a moist 10% CO_2 atmosphere. At 14 days, aggregates of more than 20 cells were counted using an inverted microscope at 50× magnification [28]. Results were expressed as mean CFU-C/10^5 cells ± standard error of the mean (SEM). Normal donor peripheral blood mononuclear cell cultures contain between zero and 25 CFU-C per 10^5 cells with a mean of six [29].

Conditioned Media

An aliquot of the patient's peripheral blood obtained at the times indicated above was incubated at 10^6 cells/ml in 20% fetal calf serum in alpha medium in 250-ml flasks (Falcon Plastics, Oxnard, CA) [24]. Supernatants were harvested after 7 days. Conditioned media were added to cultures of bone marrow cells obtained from hematologically normal, paid volunteers who gave written informed consent. Bone marrow cells were plated in the methylcellulose culture system as described for peripheral blood CFU-C assay above except that bone marrow cells were cultured at 1×10^5 cells/ml. Conditioned media comprised 20% of the total culture volume. After 14 days of incubation, colonies were quantitated as above. Colony-stimulating activity (CSA) for the conditioned media was expressed as a percent:

$$\frac{\text{mean CFU-C with test conditioned medium}}{\text{mean CFU-C with standard CSA}} \times 100$$

Statistical Analysis

All data are expressed as mean ± standard error of the mean. Comparisons were evaluated using the two-tailed Student's t-test or paired t-test.

RESULTS

Effect of Lithium Administration on Blood Counts

Myelosuppressive toxicity was evaluated during a total of 40 cycles of chemotherapy, 19 cycles on lithium and 21 cycles off. To describe fully the changes in blood counts during therapy, we determined the decline in counts from the beginning of a cycle to the lowest count in that cycle (Δ–nadir), from the beginning of a cycle to 3 weeks after treatment (Δ/cycle), and the number of days between cycles, in addition to the nadir blood counts (Tables I, II).

Paired-sample analysis was performed for 24 of the 40 cycles in which two consecutive treatments, one with and the other without lithium, were given to the patient at exactly the same chemotherapy dose (Table I). All three measures of myelosuppression—nadir, Δ-nadir, and Δ/cycle—were significantly higher during cycles on lithium for both total white blood count and neutrophil count. The nadir platelet count was also significantly higher for lithium cycles. The interval between treatments was significantly shorter (27 ± 3 days) on lithium than off lithium (38 ± 5 days) ($P<0.01$).

Blood counts during all 40 cycles of chemotherapy are summarized in Table II. The nadir leukocyte, neutrophil, and platelet counts are higher with lithium administration, but the differences are not statistically significant for the pooled data. However, the decline in both total leukocyte and neutrophil counts from the day of treatment to 3 weeks after treatment—ie, Δ/cycle—was significantly less for lithium cycles ($P<0.02$). No significant effect of lithium on platelet suppression was noted when all the data are pooled. However, if cycles of treatment in which platelet counts did not drop below 150,000/mm^3 are excluded (8 lithium and 5 nonlithium cycles, leaving a total of 27 cycles), nadir platelet counts are significantly higher with lithium administration. ($P<0.02$).

The improvement in both neutrophil and platelet suppression observed in a patient who received alternate cycles of treatment with lithium for 11 courses of chemotherapy given at 100% doses is shown in Figure 1. Neutrophil and particularly

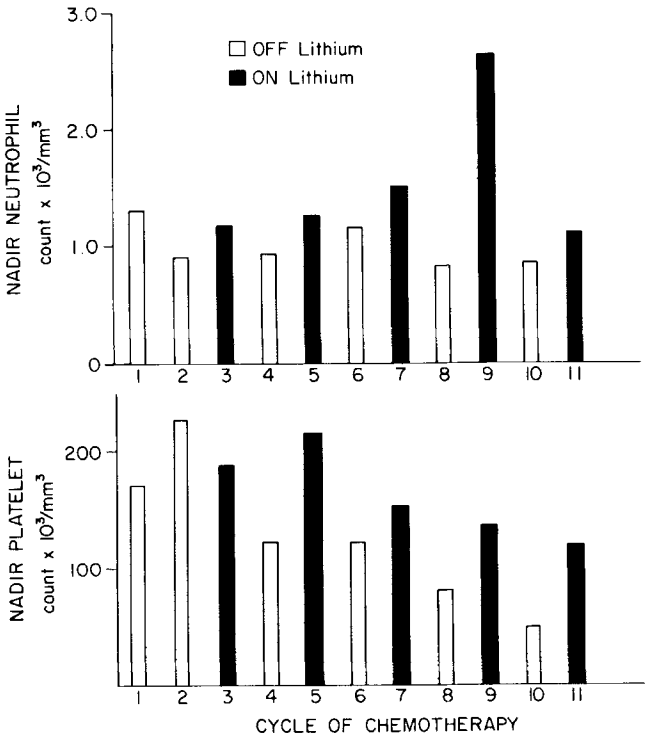

Fig. 1. Nadir neutrophil (top) and platelet (bottom) counts during 11 cycles of chemotherapy given at identical doses with or without concomitant lithium administration.

platelet nadirs were consistently higher during lithium cycles. In our total series of patients treated with this chemotherapy regimen without lithium, dose reductions to 66% of the initial level are required by the sixth cycle and no patient has been able to tolerate 100% doses by the 11th cycle without lithium administration.

Lithium had no effect on other blood counts (Table II). There was no difference in peak monocyte counts related to lithium administration. Hematocrits dropped 2.7 ± 0.7% during 19 cycles with lithium and 2.4 ± 0.9% without lithium ($P > 0.1$). The mean chemotherapy doses were not significantly different comparing 19 cycles with lithium (80 ± 5%) and 21 cycles without lithium (83 ± 4%).

Effect of Lithium Administration on CSA Production and Circulating CFU-C

Conditioned media were prepared from the patients' peripheral blood cells 3 to 4 weeks following cycles of chemotherapy and were tested using normal bone marrow target cells. A total of 27 blood samples contained sufficient cells for study of CSA production, 12 after a lithium cycle and 15 after a nonlithium cycle. There was no significant difference between the CSA content of medium following a course of therapy during which lithium was given (25 ± 5% of standard CSA) compared to a sample after a nonlithium treatment cycle (30 ± 8% of standard CSA) ($P > 0.1$, Student's t-test). In two patients, samples were obtained at more frequent intervals between cycles of treatment with and without lithium. Although CSA levels changed from week to week during the chemotherapy cycles, there was no consistent difference related to lithium administration.

Circulating granulocyte progenitors (CFU-C) are increased 3 weeks following some types of combination chemotherapy [29]. To determine whether lithium might have an effect on this process, peripheral blood was assayed for CFU-C content 3 to 4 weeks following cycles of chemotherapy. A total of 29 samples were assayed, 14 following a lithium cycle and 15 following a nonlithium cycle. The CSA used to stimulate CFU-C proliferation was a standard CSA which is effective in stimulating normal marrow CFU-C (see Methods). The peripheral blood samples studied formed no CFU-C without the addition of this CSA to the culture system. CFU-C values determined therefore reflect the concentration of committed stem cells in the circulation and do not reflect endogenous CSA production by blood cells. The mean concentration of circulating CFU-C was 3 ± 1 per 2×10^5 cells 3 to 4 weeks following chemotherapy given without lithium. Lithium administration had no effect on peripheral blood CFU-C concentration (mean CFU-C = 3 ± 1) 3 to 4 weeks following a cycle on lithium. The difference between CFU-C before and after individual cycles of chemotherapy was also not affected by lithium administration. The mean change in CFU-C was 0 ± 1 CFU-C for lithium cycles and −1 ± 1 CFU-C for nonlithium cycles ($P > 0.1$).

Toxicity of Lithium

No serious toxicity could be attributed to lithium administration. The mean lithium level was 0.80 ± 0.05 meq/liter and the highest lithium level obtained, 1.46, was not associated with any symptoms. Three patients who received a total of 17 cycles with lithium had no subjective complaints attributable to lithium. Two other patients had marked tremor (with nontoxic lithium levels) and withdrew from the study after one complete cycle with lithium. Three patients who began on the study withdrew in less than 2 weeks because of nausea and vomiting clearly exacerbated by

lithium. There was no evidence that lithium administration altered platinum nephrotoxicity. The mean creatinine clearance following 19 cycles with lithium (77 ± 5 ml/min) was not significantly different from the clearance following 21 cycles without lithium (75 ± 5 ml/min).

DISCUSSION

Lithium administration significantly decreased the depth and duration of leukopenia and neutropenia induced by chemotherapy in the present report, supporting several previous studies [10–18]. In contrast to these reports, we have documented significantly decreased platelet as well as neutrophil suppression with lithium treatment in paired cycles of chemotherapy (Table I). If we examined all 40 cycles of chemotherapy studied, the difference in platelet nadirs did not reach statistical significance (Table II). However, the paired-sample analysis permitted better control of variables which could obscure the effect of lithium on myelosuppression (eg, dose, duration of prior chemotherapy, individual variation in bone marrow tolerance). The chemotherapy regimens used by other investigators produced less thrombocytopenia than did the regimen described in the current report. For example, the mean platelet nadir both off and on lithium in one study was 186,000/mm^3 [14]. In a second study, the values were 244,000/mm^3 off lithium and 286,000/mm^3 on lithium [17]. Some studies have shown that lithium administration increases platelet counts in normal individuals [4], but other studies have not confirmed this [31]. It is possible that the salutory effect of lithium on platelet production may be apparent only if the drug regimen used produces significant thrombocytopenia. A preliminary report by Catane et al [11] showed a beneficial effect of lithium on chemotherapy-induced thrombocytopenia in ten patients with prostatic carcinoma, five of whom were randomly assigned to receive lithium with their first course of chemotherapy. Interpretation of this study is difficult, however, since many of the patients had received prior chemotherapy and/or radiotherapy and there was no documentation of lithium levels in the lithium-treated patients. Stein et al [31] have shown that the neutrophilia produced by lithium in normal individuals generally requires a dose of ≧900 mg/day and is seen only when the serum level is ≧0.55 meq/liter.

No effect of lithium on erythropoiesis could be determined in the present study, confirming previous reports [14,17]. However, because of the long half-life of red blood cells and the need for occasional red cell transfusions, it is impossible to evaluate fully the effect of lithium on erythropoiesis when the drug is given intermittently. To address this question, long-term lithium administration would have to be used. In one study in which patients were randomly assigned to receive lithium with each course of chemotherapy or to receive no lithium, there was no apparent difference in hemoglobin or hematocrit for the two groups [16,17]. However, detailed data were not presented, so it is impossible to determine whether the regimen used produced significant anemia. In contrast to the report of Lyman et al [16], we were unable to detect any significant difference in midcycle monocytosis during cycles with lithium. These findings are in agreement with those of Stein et al [14].

No effort to escalate drug doses was attempted in the present study. However, in the paired comparisons of cycles given to individuals when drug doses given on consecutive cycles with and without lithium were identical, the interval between

cycles was significantly shorter for the cycles in which lithium was administered. This suggests that the total dose of drugs administered in a given amount of time could be higher when lithium is administered. The patient whose blood counts are depicted in Figure 1 has been able to continue on 100% chemotherapy doses primarily because she was maintained on continuous lithium beginning with cycle 11.

Although lithium administration may ameliorate chemotherapy-induced myelosuppression, decrease febrile complications [16], and increase total dose administered and perhaps response rate [17], its general use as an adjunct to chemotherapy may in fact be quite limited. Although other studies have reported minimal toxicity attributable to lithium, the drug was discontinued in nine of 20 patients treated in one study because of toxic effects or patient refusal, and the median duration of lithium administration for the 20 patients was only 15 weeks [17]. In the present report, three patients were unable to take lithium for more than 2 weeks, owing to exacerbation of nausea and vomiting. Because we were employing a platinum-containing regimen known to produce significant nausea and vomiting, it is possible that mild gastrointestinal symptoms induced by lithium could be more obvious in our study than in prior studies in which platinum was not used. In addition, two of five patients who were studied asked to withdraw after one complete course with lithium because of bothersome tremor. Some reports have suggested an increased risk of cardiovascular complications with lithium administration. In our study with intermittent lithium treatment, we observed no cardiovascular problems. Lithium is known to cause nephrotoxicity, generally interstitial nephritis [33,34]. In our patients who were receiving the nephrotoxic drug platinum, there was no difference in the creatinine clearance in the 2 to 3 weeks following a cycle of chemotherapy related to lithium administration. Since the patients were treated only intermittently with lithium, this does not, however, eliminate the possibility of additive nephrotoxicity should both agents be used chronically. Additional controlled trials will be needed to define the overall benefits versus risks of lithium administration with chemotherapy. Adding a drug with many intrinsic side effects to chemotherapy which already has significant toxicity may not prove beneficial for every patient.

Lithium enhances the production of colony-stimulating factor (CSF) in normal subjects both in vitro and in vivo, as shown previously by our group and others [19–24]. Chemotherapy alone may also cause alterations in CSA production [35]. In the present study, no significant effect of lithium treatment during chemotherapy on CSA production by peripheral blood mononuclear cells was seen. However, chemotherapy-related changes in CSA production could have masked any modest changes caused by lithium.

Although lithium has been shown to increase CSA production in various studies, it is unclear that this is the only, or even the major, mechanism by which lithium stimulates granulocyte production. Several studies have shown that administration of the drug to animals, either in vitro or in vivo, can increase the number of committed granulocyte progenitors (CFU-C), perhaps because of enhanced CSA production [25,26]. However, the number of pluripotential stem cells, as assessed by the CFU-S assay, is also increased [26]. In addition, studies by Hammond and Dale [25] suggest that in vivo lithium administration to dogs with cyclic neutropenia must effect the pluripotential stem cells, since cycling of reticulocytes and platelets are abolished in addition to abolition of neutrophil, CFU-C, and monocyte cycling. In this disorder,

lithium's major effect may be on the CFU-C itself or on the pluripotential stem cells and not primarily on CSA production.

Increased concentrations of circulating CFU-C have been observed several weeks following certain forms of myelosuppressive chemotherapy [29]. This is thought to represent a "spillover" from the increased CFU-C formation in the bone marrow. In the present study, no significant change in PB CFU-C was noted with chemotherapy, and there was no apparent effect of lithium on circulating CFU-C. The drug regimen used in the present study produces cumulative toxicity with both neutropenia and thrombocytopenia, in contrast to the regimen used in the previous study in which a cyclic increase in PB CFU-C during recovery from myelosuppression was noted [29]. In the latter treatment regimen, there was a transient, deep depression of leukocyte and neutrophil counts with only minimal thrombocytopenia and less cumulative marrow toxicity. Although no change in PB CFU-C was noted in the present study, it is possible that lithium may have altered marrow CFU-C concentrations.

Lithium administration in vitro in a murine long-term bone marrow culture sytem results in gradual depletion of pluripotential stem cells (CFU-S) [26]. This obviously raises the concern that lithium administration might be associated with transient benefits followed by chronic prolonged marrow toxicity. In the study by Lyman et al [17] 20 patients given lithium in conjunction with their chemotherapy showed no evidence of cumulative marrow toxicity and in fact were able to tolerate higher doses of chemotherapy than the control group that did not receive lithium. The persistent beneficial effect of lithium shown in Figure 1 through 11 cycles (nearly 1 year) of chemotherapy suggests that there is little or no depletion of stem cells, although no firm conclusion regarding longer term effects can be made from this study.

Lithium decreases chemotherapy-induced suppression of leukocytes, neutrophils, and platelets. The effect on platelets is most pronounced when chemotherapy produces thrombocytopenia. It is possible that lithium's major effect is to enhance neutrophil production by increasing CSA production [19–24] and perhaps by a direct effect on the stem cells [37]. However, when platelets are below normal, lithium may also act on the pluripotential stem cell to enhance platelet production. Alternatively, lithium could increase platelet production via a direct or indirect effect on progenitor cells committed to megakaryocyte differentiation as suggested by murine studies [38]. Although lithium has toxicity and unknown long-term effects, it may be particularly helpful in patients who have poor marrow tolerance and would otherwise receive reduced chemotherapy doses. Since dose is one of the most important determinants of response to chemotherapy [39], lithium could increase dose tolerance and thus the chance of responding to chemotherapy in these patients.

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