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A Phase 1 and Pharmacokinetic Clinical Trial of Paclitaxel for the Treatment of Refractory Leukemia in Children: A Children's Oncology Group Study

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Abstract

Background—This report summarizes a Phase 1 study conducted by the Children's Cancer Group (CCG) to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), pharmacokinetics, and preliminary anti-leukemia activity of paclitaxel in children with advanced stage leukemias.

Procedure—This study examined two dose escalation schedules of intravenous paclitaxel. Doses ranged from 250 to 500 mg/m² every 21 days in schedule A and 105 to 200 mg/m² weekly x 3 every 28 days in schedule B. Serial plasma samples for pharmacokinetic studies were obtained after the first paclitaxel dose.

Results—Sixty-three patients (median 10 y) with refractory or relapsed leukemia [ALL (n = 39), AML (n = 19), biphenotypic (n = 4) and JCML (n = 1)] were enrolled. The DLTs in Schedule A were Grade 4 hypertension and hyperbilirubinemia with an MTD of 430 mg/m² every 21 days. The DLTs in Schedule B were coagulopathy, hyperkalemia, hyperbilirubinemia, elevated SGOT (n = 1; 125 mg/m²); peripheral neuropathy (n = 1, 200 mg/m²); and typhilitis (n = 1, 200 mg/m²) with an MTD of 182 mg/m² weekly x 3 every 28 days. Among 54 evaluable patients there was 1 complete response, 3 partial responses, and 5 patients with stable disease. The mean terminal elimination half-life was 9.5 ± 3.4 h and the mean plasma clearance was 23 ± 11 L/h/m².

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Conclusions—Paclitaxel was tolerated at 430 mg/m² every 21 days and at 182 mg/m²/dose weekly x 3 every 28 days in pediatric patients. The objective response rate across all dose levels and schedules was < 10%.

Keywords

taxol; pediatric; lymphoblastic; myelogenous; ALL; AML

INTRODUCTION

Although cure rates for children with newly diagnosed leukemia approach 85–90% for acute lymphocytic leukemia (ALL) and exceed 50% for acute myeloid leukemia (AML), the prognosis for children with relapsed leukemia remains poor and novel treatment approaches are needed for these patients. Paclitaxel, a diterpenoid that inhibits cancer cell growth by interfering with microtubule depolymerization, is approved for use in combination chemotherapy for advanced ovarian cancer, non-small cell lung cancer, and node-positive breast cancer (reviewed in [1;2]).

Previous studies have suggested that paclitaxel has activity against both acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) *in vitro* [3;4]. Paclitaxel has been shown to potently inhibit growth proliferation of HL-60 and U937 AML cell lines and primary pediatric AML and ALL cells. [4;5] In addition, it appears to enhance the cytotoxic effects of cytarabine *in vitro* [5].

The most commonly utilized dosing schedules for paclitaxel in adults include a single 24-hour (h) continuous infusion [6–8] given every 21 days and a 3-h infusion administered weekly x 3, every 28 days[9]. The MTD of 24-h continuous infusion paclitaxel was 390 mg/m² while the MTD for the 3-h weekly x 3 schedule was 100 mg/m²/dose. The DLT was grade 3 mucositis or stomatitis.

Several schedules of paxlitaxel administration have been evaluated in children with solid tumors.[7;10;11] Hurwitz et al. administered single-dose paclitaxel every 21 days in doses ranging from 200 to 420 mg/m² [7]. The DLT was neurotoxicity and the recommended phase 2 dose was 350 mg/m². Hayashi et al. administered paclitaxel twice weekly for 6 doses every 28 days and recommended a paclitaxel dose of 65 mg/m²/dose (390 mg/m²/course)[10]. Sonnichsen et al. administered single-dose paclitaxel (200 to 420 mg/m²) to 30 pediatric patients with refractory solid tumors and noted saturable distribution and elimination mechanisms, explaining a large variability in paclitaxel exposure based on dose [12]. A follow up phase 1 study tested an alternative, single-dose paclitaxel schedule in 7 pediatric patients with recurrent pediatric leukemia using a pharmacokintetically-guided dosing strategy, targeting an AUC of 21–45 µM*h (28–38 µg/ml*h) [11]. The DLT in this study was mucositis [11]. The most effective dosing schedule for children with leukemia has not been determined. This report describes the results of phase 1 study of paclitaxel for pediatric patients with leukemia that evaluated single-dose every 21 days (Schedule A) and weekly x 3, every 28 days (Schedule B) schedules of paclitaxel administration.

METHODS

Patient Eligibility

Patients ≥ 21 years of age at the time of original diagnosis with a histologically confirmed diagnosis of ALL, AML, or chronic myelogenous leukemia (CML) (>25% leukemia blast involvement) refractory to standard therapy, were eligible for this trial. Additional eligibility requirements included an ECOG performance status of 0, 1, or 2; life expectancy ≥ 2 months; full recovery from the acute toxic effects of prior chemotherapy and radiotherapy, with at least 2 weeks since prior chemotherapy excluding steroids (4 weeks from prior nitrosourea therapy), and no prior treatment with paclitaxel; normal renal function; adequate liver function (total bilirubin ≤ 2 times the upper limit of normal [ULN], AST and ALT < 2.5 times ULN); and adequate cardiac function (normal EKG and either shortening fraction ≥ 27% by echocardiogram or ejection fraction ≥ 50% by gated radionuclide study). All patients or their legal guardians provided written informed consent in accordance with institutional, FDA, and NCI policies.

Drug Administration

The starting dose of paclitaxel administered every 21 days over 24 h (Schedule A) was 250 mg/m²/dose, 80% of the recommended adult starting dose [13]. Doses were escalated in 20% increments to a maximum 500 mg/m²/dose. A single patient cohort received 250 mg/m²/dose paclitaxel every 14 days (Schedule A1) to confirm the safety of more frequent administration of taxol. The dose escalation schedule was then modified to administer paclitaxel weekly for three consecutive weeks, every 28 days (Schedule B). The starting dose for Schedule B was 105 mg/m²/dose (75% of the pediatric leukemia single-dose taxol MTD divided by 3) and was increased over 6 dose levels to a final level of 200 mg/m²/dose. Subsequent cycles of paclitaxel were administered in patients with stable or better disease if all grade 3 toxicities had resolved to ≤ grade 2 within 2 weeks of the time that the next course was scheduled to begin. Doses were not held or omitted for hematologic toxicity.

A minimum of three patients were entered at each dose level and if one patient experienced DLT during the first cycle of therapy then the dose level was expanded to include up to six patients. The MTD was exceeded when dose-limiting toxicity was observed in two patients of a cohort of three to six patients receiving the same dose of drug. The MTD of paclitaxel was defined as the dose level immediately below the level at which at least two patients experienced dose-limiting toxicity. Patients were considered evaluable for DLT if they received at least one dose of paclitaxel. DLT was defined as a non-hematologic, non-resolving grade 3 paclitaxel-related adverse event or non-hematologic grade 4 paclitaxel-related adverse event that occurred during the first course. Toxicities were graded according to National Cancer Institute Common Toxicity Criteria, v. 2.0.

Response

Patients were considered evaluable for response if they received at least one complete dose of paclitaxel, and had either at least one bone marrow evaluation during protocol therapy or had clinical evidence of progressive disease prior to stopping protocol therapy. A complete response (CR) was defined as a bone marrow with < 5% leukemia cell infiltrate and no

evidence of circulating blasts or extramedullary disease, recovery of absolute neutrophil count (ANC) to $>1000/\text{mL}$ and recovery of platelet count to $>100,000/\text{mL}$. Partial response (PR) was defined as a bone marrow with $\leq 5\%$ and $<25\%$ leukemia cell infiltrate, and complete disappearance of circulating blasts with ANC and platelets recovery. Progressive disease (PD) was defined as an increase of at least 25% in the number of circulating blasts or bone marrow leukemia cell infiltrate, or the development of extramedullary leukemia. Stable disease (SD) was defined as any patient not meeting the criteria of CR, PR, or PD. Response was determined at the end of cycle 1.

Study Drug

Paclitaxel was supplied in 5 mL ampules containing a concentrated sterile solution of 6 mg/mL in 50% polyoxyethylated castor oil (Cremophor EL) and 50% dehydrated alcohol from the Cancer Therapy Evaluation program (CTEP), (NCI, Bethesda, MD). Study drug was diluted to a final concentration of 0.3 mg/mL to 1.2 mg/mL in either D₅W or normal saline. Paclitaxel was administered as a continuous, 24-h intravenous infusion. Patients were premedicated with dexamethasone (20 mg/m² for 2 doses), diphenhydramine (1 mg/kg) and ranitidine (0.5 mg/kg) prior to paclitaxel administration.

Pharmacokinetics

Blood samples were collected from a peripheral vein remote from the chemotherapy infusion site into heparinized tubes at the following time points: pre-infusion, 2, 4, 8 and 16 hours (h) during the infusion, end of infusion, and 15 minutes (min), 30 min, 1, 1.5, 2, 3, 4, 8, 16 and 24 h after the end of the infusion. Plasma supernatants were frozen at -70°C until analysis. Paclitaxel plasma concentrations were measured using high pressure liquid chromatography as previously described[14]. The UV absorbance signal peak height ratio (paclitaxel/N-cyclohexylbenzamide internal standard) was analyzed by linear least-squares regression. The pharmacokinetics of paclitaxel were estimated using the program WinNonlin Version 1.5 (Pharsight Corporation, Mountainview, CA). Distribution (α) and elimination (β) rate constants and half-life values ($t_{1/2\alpha}$ and $t_{1/2\beta}$), $\text{AUC}_{0-\infty}$, steady-state volume of distribution (V_{ss}) and total plasma clearance (Cl) were determined by fitting the plasma concentration-time data (during infusion and post-infusion) to a two-compartment open model using non-linear least squares regression analysis. Linear regression analysis of variance was used to assess the linear effect of taxol dose with clearance according to the model:

$$y_i = \beta_0 + \beta_1(\text{dose level in mg/m}^2) + \varepsilon_i; \varepsilon_i \sim N(0, \sigma^2)$$

RESULTS

Patient Treatment

A total of 63 patients (35 male), median age 10 years (y) (range 0.8 to 23 y), were entered on study. The majority had relapsed ALL (n = 39) or AML (n = 19). One patient died of an infection prior to treatment. Of the remaining patients, 22 were treated with single-dose paclitaxel every 21 days (Schedule A), 6 were enrolled in the cohort that received paclitaxel

every 14 days (Schedule A1), and 34 received weekly paclitaxel for 3 weeks every 28 days (Schedule B). Eight patients receiving single-dose paclitaxel received two treatment courses and 3 patients receiving weekly paclitaxel received more than one treatment course (Table I).

Toxicities

Forty-five patients were fully evaluable for toxicity. DLTs for Schedule A (q 21 day) paclitaxel were grade 4 hypertension (n=1, 430 mg/m²) and grade 4 hyperbilirubinemia (n=1, 500 mg/m² level) (Tables I and II). A second patient treated at the 500 mg/m² dose level experienced grade 4 stomatitis and diarrhea early in the second treatment course and no further dose escalations were done using this dosing schedule. DLTs with Schedule B (weekly paclitaxel x 3, every 21 days) administration included one patient who experienced Grade 4 coagulopathy, hyperkalemia, hyperbilirubinemia, and elevated SGOT (125 mg/m²/dose), grade 4 peripheral neuropathy (n=1, 200 mg/m²/dose), grade 4 stomatitis and grade 4 typhilitis (n=1, 200 mg/m²/dose). The MTD of weekly paclitaxel for 3 weeks every 28 days was 182 mg/m²/dose (Table I). A summary of all reported grade 3 and 4 non-hematologic toxicities is shown in Table II. The most frequent paclitaxel-related events were stomatitis/mucositis (3 patients), hypertension (2 patients), hyperbilirubinemia (2 patients), and elevated transaminases (2 patients).

Response

Using an intention to treat analysis, 54 of the 62 treated patients were evaluable for response (18/23 using Schedule A, 30/34 using Schedule B) (Table III). Eight patients were not evaluable for response due to early death related to progressive disease (n = 5), early withdrawal due to toxicity (n = 2), or lack of an assessable bone marrow aspirate in the absence of progressive disease following the first treatment cycle (n=1). One complete response was observed in a 15 year old (yo) male with pre-B ALL treated with weekly paclitaxel (Schedule B) using 125 mg/m²/dose. Partial responses were also observed in 2 patients with pre-B ALL treated with weekly paclitaxel using 125 mg/m²/dose and 182 mg/m²/dose (Schedule B), and one patient who received 300 mg/m²/dose every three weeks (Schedule A). Four evaluable patients had stable disease and 46 had progressive disease.

Pharmacokinetics

Single-dose paclitaxel pharmacokinetics were characterized in 17 patients and summary data are provided in Table IV. Paclitaxel plasma concentrations were best fit to a two-compartment model (Figure 1). Mean volume of distribution at steady state was 139 L/m². The overall mean distribution half-life ($t_{1/2\alpha}$) and mean elimination half-life ($t_{1/2\beta}$) for 16 of the 17 patients were 0.8 ± 0.6 hours and 9.5 ± 3.6 hours, respectively. Data for one patient with substantially prolonged elimination half-life was not included in these estimates. Mean plasma clearance was 23 ± 12 L/h/m². There was a pattern of decreasing clearance rate with increasing dose (slope = - 0.04; 95% confidence interval: -0.13–0.34, $R^2=0.11$) but this was not statistically significant (p= 0.18) (Figure 2).

DISCUSSION

In the current study, we investigated the safety and tolerability of paclitaxel in 62 children with relapsed leukemia. This study represents the largest pediatric study of paclitaxel in children. The recommended phase 2 paclitaxel dose using a single-dose of paclitaxel every 21 days (Schedule A) is 430 mg/m², which is higher than the dose tolerated in adults with solid tumors (170–250 mg/m²), [1;14] adults with leukemia (250–315 mg/m²) [13] and pediatric patients with solid tumors (350 mg/m²) [7]. This phase 2 recommended dose is based on the first course dose-limiting toxicities of hypertension and hyperbilirubinemia in one heavily pretreated post-transplant patient and the second course dose-limiting toxicity of stomatitis in another patient at the 500 mg/m² dose level. Toxicities were not substantially different than those reported in adults. Although taxol is uncommonly associated with liver toxicity, it has been previously reported {Seiter, 1995 52 /id}.

The recommended phase 2 paclitaxel dose for Schedule B (weekly x 3 weeks, every 28 days) was 182 mg/m²/dose (546 mg/m² per course), which is also higher than the weekly paclitaxel dose tolerated in adults (80–100 mg/m²/dose, 300 mg/m²/course) [9] or in children with solid tumors (65 mg/m²/dose; 390 mg/m²/course) [10]. The DLTs using a weekly dosing schedule were Grade 4 peripheral neuropathy and grade 4 typhilitis (200 mg/m² weekly), which have been previously reported as DLTs in both adults and children [7;15].

The pharmacokinetic behavior of paclitaxel in children enrolled in this trial was similar to that previously described in adults and children. The average clearance (23 L/h/m²) and volume of distribution (139 ± 108 L/m²) values in this study were similar to that reported in adults and children [7;16]. Distribution and elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$) in this study were slightly longer than those reported in adults ($t_{1/2\alpha}$ = 48 min (0.8h) vs. 4–30 min; $T_{1/2\beta}$ = 9.5 h vs. 1.5–8.4 h [16]). Although lower than expected from adult data [16], the peak plasma concentrations ($C_{\max}$) in our study (0.38 – 1.3 µg/ml) were similar to that previously reported in children [7;12].

Two previous pediatric studies have reported saturable paclitaxel pharmacokinetics, contributing to substantial interpatient variability in clearance values. [11;12] To adjust for the resulting variability in paclitaxel $C_{\max}$ and clearance at high paclitaxel doses, Woo et al. implemented a dose-individualized strategy (termed maximum tolerated systemic exposure, MTSE) based on target AUC values in 6 children with refractory leukemia [11]. Paclitaxel clearance in that study ranged from 113 to 311 mL/min/m² (6.8 L/h/m² to 18.7 L/h/m²), which was similar to the authors' previous experience with paclitaxel in children with solid tumors [12]. The average clearance for children with refractory leukemia in this study (23 L/h/m²) was moderately higher than that reported by Woo et al., but the 95% confidence interval for the mean clearance for patients enrolled on this study includes 6.8 L/h/m² indicating the results of the current investigation are consistent with these previously published results.

In this study, we observed one complete response and 3 partial responses in 62 treated patients. In an adult Phase 1 and 2 trials of paclitaxel in leukemia there was only one transient response [6] [13]. Weekly paclitaxel dosing in adults with leukemia was also found

to be ineffective[9]. In one prior pediatric study in leukemia, all 7 children treated had disease progression after 1 or 2 cycles [11]. Although this trial was not an efficacy study, the paucity of objective responses coupled with the cumulative results of other studies suggest that paclitaxel is ineffective as a single agent in the treatment of recurrent or refractory leukemia using these dosing schedules. No further development of this agent in leukemia is planned within the Children's Oncology Group.

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Figure 1. Paclitaxel plasma concentrations vs. time in pediatric patients. Paclitaxel (430 mg/m^2) was administered by 24-hour infusion. Symbols and error bars represent the mean $\pm$ standard deviation for data from 5 patients. The solid line illustrates a fit of the data to a 2-compartment open model.

Figure 2: Paclitaxel clearance vs. dose in pediatric patients:

Single-dose paclitaxel was administered to 17 pediatric patients with leukemia at 6 dose levels (250 mg/m² (n=4); 300 mg/m² (n=3); 360 mg/m² (n=2); 400 mg/m² (n=1); 430 mg/m² (n=5); and 500 mg/m² (n=2)) and clearance was determined as described (methods).

Table 1.

Demographics and disease characteristics

Characteristic	Parameter
Age (years)	
Median	10
Range	0.8 to 23
Sex (N [%])	
Male	35
Female	25
Diagnosis N (%)	
ALL	40 (39)
AML	16 (19)
Biphenotypic	3 (4)
JCML	1
Race	
Caucasian	35
Black	7
Hispanic	12
Asian (Filipino)	5 (3)
Native American	1
Other	3
Prior Therapy	
Chemotherapy	63
BMT	18
Radiation	24

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; APL acute promyelocytic leukemia; JCML, juvenile chronic myelogenous leukemia

Table 2.

Summary of Treatment with Paclitaxel

Dose and Frequency	Number of Patients Entered	Number of Courses	
		Full	Partial
250 mg/m ² q 21 d	5	8 ^a	
300 mg/m ² q 21 d	3	4 ^b	
360 mg/m ² q 21 d	3	3	
430 mg/m ² q 21 d	7	9 ^c	
500 mg/m ² q 21 d	5	6 ^d	
250 mg/m ² q 14 d × 2	6	4	2
105 mg/m ² q 7 d × 3	4	4 ^f	
125 mg/m ² q 7 d × 3	7	10 ^g	2
150 mg/m ² q 7 d × 3	4	3 ^h	1
165 mg/m ² q 7 d × 3	3	3	
181.5 mg/m ² q 7 d × 3	8	8 ⁱ	1
200 mg/m ² q 7 days × 3	8	4	5

^aThree patients received 2 courses

^bOne patient received 2 courses

^cTwo patients received 2 courses

^dOne patient was not treated; 2 patients received 2 courses

^fTwo patients received 2 courses

^gOne patient received 3 courses and another patient received 4 courses.

^h3 patients received full course, one patient received one dose only

ⁱOne patient received 2 courses; 1 patient received only a partial course

Table 3.

Grade 3 and 4 Non-Hematologic Toxicities (regardless of attribution)

Dose	Number of Patients With DLT/Total evaluable	Number of Events	Number of DLTs	Number of Patients with DLT	Description of Events, by patient
250 mg/m ²	2/3	3	0	0	1) Grade 3 bilirubin and Grade 4 infection 2) Grade 3 pancreatitis
360 mg/m ²	1/3	1	0	0	Grade 4 hemorrhagic cystitis
430 mg/m ²	2/4	2	1	1yes	1) Grade 4 hypertension (DLT); 2) Grade 4 infection (E. coli and CONS sepsis)
500 mg/m ²	3/3	4	1	1	1) Grade 4 bilirubin (DLT); 2) Grade 4 pulmonary infiltrates; 3) 2 nd cycle: Grade 4 stomatitis and diarrhea
125 mg/m ² q7d × 3	5/5	10	4	1yes	1) Grade 4 coagulopathy (DLT), hyperkalemia (DLT), elevated bilirubin (DLT), and elevated SGOT (DLT) 2) Grade 4 infection (E. coli sepsis) and hyperbilirubinemia, Grade 3 mucositis and elevated transaminases (ALT); 3) Grade 4 hyperglycemia and nausea/vomiting; 4) Grade 4 hyperglycemia 5) Grade 4 infection (Klebsiella sepsis) and Grade 3 hypertension (resolved)
181.5 mg/m ² q7d × 3	3/5	1	0	0yes	1) Grade 4 Infection (E. coli sepsis) 2) Grade 3 hyperbilirubinemia and elevated transaminases (ALT/AST) 3) Grade 3 hyperglycemia (resolved)
200 mg/m ² q7d × 3	4/?	7	2	2	1) Grade 4 hypertension; 2) Grade 3 hypertension (resolved) 3) Grade 4 hypotension with infection (2 patients); 3) Grade 4 typhilitis (DLT), rectal pain/stomatitis (DLT); 4) Grade 5 infection (pneumonia); Grade 4 bilirubin, pulmonary infiltrates, and hypotension.; grade 3 elevated transaminases (ALT), hyperkalemia and hyperglycemia.

Table 4.

Summary of Responses to Paclitaxel

Dose and Frequency	Number of Patients	Responses				
		CR	PR	SD	PD	NE
250 mg/m ² q 21 d	5	0	0	0	3	2
300 mg/m ² q 21 d	3	0	1	0	2	0
360 mg/m ² q 21 d	3	0	0	0	3	0
430 mg/m ² q 21 d	7	0	0	1	5	1
500 mg/m ² q 21 d	5	0	0	0	2	3
250 mg/m ² q 14 d × 2	6	0	0	0	5	1
105 mg/m ² q 7 d × 3	4	0	0	0	3	1
125 mg/m ² q 7 d × 3	7	1	1	0	3	2
150 mg/m ² q 7 d × 3	4	0	0	0	2	2 ^g
165 mg/m ² q 7 d × 3	3	0	0	0	3	0
181.5 mg/m ² q 7 d × 3	8	0	1	0	7	0
200 mg/m ² q 7 days × 3	8	0	0	1	4	3
All doses	63	1	3	2	42	15

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease

Table 5:
Pharmacokinetic parameters.

The AUC mean $\pm$ standard deviation (SD) The clearance and volume of distribution are dose-independent and are averaged for the entire group. Medians used for any parameter with <3 data points.

Dose Level (mg/m ²)	Patient	AUC ($\mu\text{g/ml}\cdot\text{h}$)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	C_{max} ($\mu\text{g/mL}$)	CL (L/h/m ²)	V_{ss} (L/m ²)
250	1	7.0	0.32	7.8	0.29	36	154
	2	15.4	0.72	14.7	0.55	16	159
	3	6.5	0.61	4.8	0.26	39	167
	4	11.1	0.71	6.8	0.44	23	105
	Mean +SD	10 $\pm$ 4.1	0.6 $\pm$ 0.2	8.8 $\pm$ 5.2	0.38 $\pm$ 0.13	28 $\pm$ 11	146 $\pm$ 28
300	1	19.1	1.60	15.5	0.74	16	124
	2	24.4	0.37	6.8	0.99	12	38
	3	5.8	0.31	9.4	0.21	52	445
	Mean + SD	16.4 $\pm$ 9.6	0.8 $\pm$ 0.7	10.6 $\pm$ 4.4	0.65 $\pm$ 0.4	26 $\pm$ 22	202 $\pm$ 214
360	1	12.8	0.46	10.1	0.45	28	175
	2	34.5	0.32	6.1	1.42	10	18
	Median	23.6	0.39	8.1	0.93	19	96
400	1	18.6	0.73	9.9	0.74	23	101
430	1	25.6	0.99	10	0.95	17	150
	2	28.4	0.63	9.9	1.15	16	47
	3	11.5	2.19	13.6	0.44	38	305
	4	28.5	1.72	13.8	1.07	15	117
	5	18.1	0.47	5.3	0.73	24	88
	Mean+ SD	22.4 $\pm$ 7.4	1.2 $\pm$ 0.7	10.5 $\pm$ 3.4	0.87 $\pm$ 0.28	21 $\pm$ 9.5	141 $\pm$ 100
500	1	26.8	1.76	230	0.73	19	2315
	2	45.0	0.49	6.9	1.81	11	27
	Median	36	1.1	118	1.3	15	1171
Mean			0.85 $\pm$ 6	9.5 $\pm$ 3.4		23 $\pm$ 11	0.85 $\pm$ 0.59