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A Phase I Study of Heat Deployed Liposomal Doxorubicin during Radiofrequency Ablation for Hepatic Malignancies

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Abstract

PURPOSE—A phase I dose escalation study was performed with systemically delivered lyso-thermosensitive liposomal doxorubicin (LTLD) (Celsion Corp., Columbia, MD). The primary objectives were to determine the safe maximum tolerated dose (MTD), pharmacokinetic (PK) properties, and dose limiting toxicity (DLT) of LTLD during this combination therapy.

MATERIALS AND METHODS—Subjects eligible for percutaneous or surgical RFA with primary (n=9) or metastatic (n=15) tumors of the liver, with lesions 4 or less in number and up to 7 cm in diameter were included. RFA was initiated 15 minutes after starting a 30 minute intravenous LTLD infusion. Dose levels between 20 and 60 mg/m² were evaluated. MRI, PET and CT scans were performed at predetermined intervals pre and post-treatment until evidence of recurrence, administration of additional antitumor treatment, or a total of 3 years.

RESULTS—DLT criteria were met at 60 mg/m², and the MTD was defined as 50 mg/m². RFA was performed during the peak of the plasma concentration-time curve, in an effort to yield maximal drug deposition. LTLD produced reversible, dose-dependent neutropenia and leukopenia.

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BW conceived of the experiment, initially conceived of combining heat sensitive liposomal chemotherapy with RFA, and conceived of the rational and timing for co-administration of drug and device. SL conceived of the drug dosages and BW and SL alone wrote the Phase I clinical trial protocol. BW drafted the study concept; wrote the first draft of the protocol; and wrote and prepared the first draft of the manuscript with outline guidance from SL.

Disclaimers

The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

CONCLUSION—LTLD can be safely administered systemically at the MTD (50 mg/m²) in combination with RFA, with limited and manageable toxicity. Further evaluation of this agent combined with RFA is warranted to determine its role in the management of liver tumors.

Introduction

Thermal ablation techniques such as radiofrequency ablation (RFA) have been widely used for unresectable liver tumors; however, residual or recurrent disease is often found at the treatment margin. A wide variability in local failure rates has been reported with RFA systems for the treatment of primary and metastatic liver tumors [1–4]. For example, local progression rates after RFA for tumors < 3 cm in diameter ranges from 1.8–52.8% [3–6]. For tumors > 3 cm however, the local failure rate for RFA increases markedly, as high as 75% [1–4, 7–9]. In a meta-analysis of 5224 liver tumors treated by RFA, tumor size > 3 cm was one of the most important risk factors for local recurrence [10]. Equipment and techniques for thermal ablation continue to evolve in an effort to create more uniform and larger thermal lesions in order to address treatment failure at the margin.

Recurrences at the margins of the treated lesions are most likely due to areas of untreated microscopic disease. It is possible that this zone of microscopic disease could be effectively treated by combining chemotherapy with RFA [11]. The challenge is to minimize the systemic toxicity of chemotherapy and to maximize its local delivery to the region immediately surrounding the liver tumor during RFA, which remains viable, but is exposed to non-lethal increases in temperature. In related experiments, mild hyperthermia (39–40°C) not only improved the release of doxorubicin encapsulated in lyso-thermosensitive liposomes (LTSL), but also increased doxorubicin attachment to DNA and RNA of tumor tissue in a human tumor xenograft model [12]. Furthermore, >10 times more doxorubicin was detected just outside the thermal lesion than remote unheated tissue in swine liver in vivo when LTSL encapsulated doxorubicin was administered intravenously during RFA [13]. Local image guided drug delivery is possible by combining ablative devices with heat deployed chemotherapy. Lyso-thermosensitive liposomal doxorubicin (LTLD) (ThermoDox®, Celsion Corp., Columbia, MD) has been developed to release doxorubicin at temperatures > 39.5°C, the same temperature range as is present in tissue immediately surrounding the thermal ablation zone, in both mathematical modeling and in vivo studies [14]. When LTLD is combined with RFA, the drug may be deposited precisely in the location of most common treatment failure, this thermal margin. There are very limited data on RFA combined with systemic or regional therapeutics, but prior work suggests non-heat sensitive liposomal doxorubicin may increase the volume of ablation [11]. Prior work showed that doxorubicin remains cytotoxic in tissue culture when it is heated in the typical range of time and temperature as with RFA [see supplemental information]. This drug plus device paradigm of ablative devices combined with heat-deployed chemotherapy directly addresses the high rate of local failure of RFA especially in large tumors by selectively depositing chemotherapy at the thermal margin where it is most needed.

To evaluate the safety and feasibility of this drug plus device combination, a phase I dose escalation study of LTLD administered during RFA of unresectable hepatic malignancies was performed. The primary objectives were to determine the safe maximum tolerated dose (MTD), pharmacokinetic (PK) properties, and dose limiting toxicity (DLT) of LTLD administered systemically in conjunction with thermal ablation.

Materials and Methods

All patients underwent written informed consent and the study was approved by the Investigational Review Boards and the United States Food and Drug Administration as part of an Investigational New Drug evaluation.

Patient Selection

Patients with unresectable primary or metastatic liver neoplasms, with no more than 4 lesions, each with diameters not greater than 7 cm were eligible. Systemic therapy for extrahepatic disease was not allowed 21 days before enrollment nor 28 days after treatment. Standard exclusion criteria for doxorubicin use and laboratory values were defined (see supplement). Drug Formulation and Treatment Schema

A single on-site pharmacist prepared the LTLD to the specified concentration according to manufacturer's guidelines. Additional details may be found in supplemental information. Dosing was carried out using the subject's body surface area (BSA m²); calculated using Boyd's formula. A 3 + 3 dose escalation design was utilized and six dose levels were planned: 20, 30, 40, 50, 60 and 70 mg/m², each with 3 to 6 patients per dose level. The MTD was defined as the dose at one level below that maximum achieved dose in which 2 patients exhibited DLT (Table 1). Once the MTD was defined, additional patients were entered at the MTD for a total of 6 patients at that dose level. Therefore, no more than 1 patient in 6 would exhibit DLT at the MTD.

Pre-Procedure

Standard pre-treatment evaluation included contrast-enhanced CT scans, vital signs, serum chemistries, complete blood counts, liver function tests, coagulation panels, electrocardiogram, and a Multi Gated Acquisition Scan (MUGA) or echocardiogram. Maximum lifetime dose of doxorubicin was limited to <500mg/m².

All patients received prophylaxis against immediate hypersensitivity reactions. Beginning 48 hours prior to treatment, subjects received dexamethasone (APP Pharmaceuticals, Schaumburg, IL) 10 mg po every 12 hours × 4 doses and ranitidine (GlaxoSmithKline, Philadelphia, PA) 150 mg po every 12 hours × 4 doses. Thirty minutes prior to starting study drug, dexamethasone 20 mg IV, diphenhydramine (Baxter, Deerfield, IL) 50 mg IV, and ranitidine 50 mg IV were administered. Two standard venous access devices or IVs were placed for PK blood draws and drug administration.

Intraprocedure

A single dose of LTLD was infused via a peripheral IV over 30 minutes. RFA was initiated 15 minutes after the LTLD infusion began. RFA was performed using standard algorithms with a commercial 200 watt generator, and water-cooled electrodes (Covidien, Inc., Boulder, CO). All procedures were performed with patients under general anesthesia.

To prevent systemic drug release due to the potential of increasing body temperature during RFA, patients were prophylactically placed on a full body cooling blanket (Gaymar Industries, Inc., Orchard Park, NY) with additional cooling blankets (Cincinnati Sub-Zero, Cincinnati, Ohio) wrapped around both thighs to cover the grounding pads and to avoid heating of the skin. Skin temperatures were monitored continuously under the cranial edge of the 2 anterior grounding pads during the procedure. In addition, a temperature sensing foley catheter (C.R. Bard, Inc. Covington, GA) was inserted to assess core body temperature. Cooling blankets were turned on when systemic temperatures reached 38°C or

when grounding pads approached 35°C (documented in 11/24 subjects). For percutaneous procedures, an immediate post procedure enhanced CT scan was performed.

Post-Procedure

Monitoring for treatment-related toxicity included inpatient observation for at least 48 hours, blood and urine collection for PK, temperature monitoring, physical findings, vital signs, adverse events and standard chemistry and hematologic laboratory parameters. Since the half-life of LTLD administered systemically and released by RFA was not previously defined, oral or tympanic temperatures were monitored every 4 hours for 48 hours to avoid full-body triggered release of drug. Patients were discharged with mail-in packages for further serum and urine samples. Evaluations were performed during the first 24 hours, at 48 hours and on Days 4, 8, and 14 (± 2 days) and as clinically indicated. Patients whose lab values became abnormal and had not returned to grade 1 (or baseline) had those labs repeated on Day 14 (± 2 days). All patients were seen in the clinic 28 ± 5 days post-treatment or more frequently if clinically indicated. Patients were evaluated on Day 28 ± 5 using MRI, PET, and contrast enhanced CT studies to assess the effects of therapy per standard of care. Imaging and laboratory assessments were repeated at 3 month intervals (± 5 days) for the first year and then at 6 month intervals until evidence of recurrence, administration of additional antitumor treatment, or a total of 3 years. Repeat RFA without LTLD was allowed subsequent to the Day 28 assessment for recurrent hepatic (new sites or local) tumors. Only lesions treated with RFA plus LTLD were included in response assessments.

Since neither RECIST nor WHO criteria apply to thermally ablated lesions, imaging response was determined by standard radiological criteria including thermal lesions' size and location, rim enhancement characteristics, presence of nodular enhancement, PET standardized uptake values at the margin, and change over time [15].

Pharmacokinetic Methods

See supplemental information for plasma and urine sampling methods. Plasma concentration-time data for total doxorubicin and doxorubicinol were analyzed by non-compartment methods [16, 17]. Plasma and urine PK parameters were derived using standard software (WinNonLin 4.1 (Pharsight; Mountain View, CA)). Area under the plasma concentration curves (AUCs) were calculated using the linear trapezoidal rule up to the maximum plasma concentration, and thereafter using the logarithmic trapezoidal rule. AUC was calculated to the last measurable plasma concentration and the remaining area was extrapolated to infinity $AUC_{0-\infty}$. The terminal exponential phase data points were determined by visual inspection of the plasma concentration-time profiles and λ_z values were calculated by log-linear regression of terminal exponential phase data points.

Statistical methods

Descriptive statistics (mean, standard deviation (SD), percent coefficient of variation (%CV), median, minimum and maximum) were calculated for maximum plasma concentration (C_{max}), area under the plasma concentration-time profile from time zero to infinity ($AUC_{0-\infty}$), clearance (CL) and volume of distribution at steady state (V_{ss}) for total doxorubicin and doxorubicinol from all subjects (see supplemental information). The effects of dose were co-analyzed with hematological toxicity and adverse events using linear regression (Microsoft Excel, 2003) and the exact Jonckheere-Terpstra test.

For the 50 mg MTD cohort, additional analyses were performed, including an estimation of the effect of intermittent RFA. The overall RFA time, defined as from the start of the first

RFA to the end of the last, and RFA intermittent time were calculated and examined in relation to the calculated doxorubicin $AUC_{0-\infty}$.

Results

Table 2 summarizes baseline demographics and treatment characteristics. Most subjects (62%) had tumors > 3 cm; the largest diameter was 6.5 cm (mean= 3.6 and range=1.7–6.5 cm). Six patients were retreated with RFA (without drug) at a later date. There were 2 DLTs at the 60 mg/m² dose level: a grade 3 alanine aminotransferase (ALT) increase and a grade 4 neutropenia. There was a single DLT (grade 4 neutropenia) in the 50 mg/m² cohort, establishing this as the MTD. All three DLTs were reversible.

Two subjects had cirrhosis with mildly abnormal transaminases before treatment, which remained less than grade 2 throughout the study. The first subject was in the 20mg cohort and had baseline AST 54 U/L (normal range 9–34), ALT 52 U/L (normal range 6–41), and neutrophil 92.8% (normal range 40–78) with 18.189 k/mcL (normal range 1.32–7.5). The second subject was in the 60mg cohort and had baseline AST of 48 U/L, ALT 28 U/L, and neutrophil 57.7% with 3.641 k/mcL. The pretreatment neutrophil count was within normal limits (WNL) and was grade 4 days 11 through 16. Five days of neutropenia requiring Filgrastim was a DLT. This patient received Filgrastim on days 16–22 and recovered to grade 1 by day 17, and was the only patient with febrile neutropenia.

Focusing on the MTD (50 mg/m² cohort) shown in Figure 1, the concentration of doxorubicin peaked at 30 minutes and then decreased as doxorubicin was cleared (initial half-life 0.92 hr) from the plasma. More than 92% (range 84.6 – 93.9) of the entire plasma $AUC_{0-\infty}$ for doxorubicin occurred in the 3.5 hours post-infusion. Consistent with liposomal therapies, the total body clearance of doxorubicin was 1.1 L/h/m² (range 0.84–1.41) much slower than the clearance of doxorubicin = 30.2 L/h/m² [18]. Similarly, the Vss of ~5.1 L/m² (range 3.26–9.76), which approximates 1.75 times the standard blood volume, was also much smaller than doxorubicin ~ 947 L/m² [18]. These data suggest that doxorubicin associated with LTLD therapy is largely contained within the blood compartment.

Taking advantage of LTLD PK, RFA was initiated 15 minutes into the 30 minute infusion (depicted in Figure 1) in an effort to gain the greatest release of doxorubicin within the thermal margin, or in other words, by maximizing the doxorubicin $AUC_{0-\infty}$ associated with the RFA procedure. RFA for large liver tumors applies intermittent current in standard practice. In the MTD cohort (50 mg/m²), the overall RFA time was 2.1 hr (range = 0.85–3.15hr) with RFA current on 56% of the overall RFA time (range = 44–81%). This intermittent application of RFA captured 51% (range = 41–74%) of the $AUC_{0-\infty}$ and the overall RFA time captured 90% (range = 82–93%) of the $AUC_{0-\infty}$.

No cases of decreased ejection fraction, congestive heart failure (associated with doxorubicin), renal failure or hand-foot syndrome (associated with liposomes) were observed and no renal toxicity was seen. Only one sensitivity reaction (pruritis) occurred with LTLD administration. Two patients had grade 4 neutropenia lasting 7 days each and requiring pharmacologic stimulation (each considered a DLT). The most frequent drug related adverse events from all grades are summarized in Table 3.

The onset of neutropenia most likely associated with LTLD tended to be slightly delayed, with the grade 4 toxicity appearing at day 9 and day 11, whereas liver function tests (ALT and AST) most likely associated with RFA effect tended to peak earlier (day 2 for grade 3 ALT elevation). Elevations of ALT and AST are expected following RFA, but with insufficient data here to discriminate causal factors, these toxicities were considered in the DLT evaluation. Selected adverse events were tested for relationship to LTLD dose.

Neutropenia $P = 0.0011$, leukopenia ($P = 0.0043$), and alopecia ($P = 0.0148$) were dose-dependent while elevated ALT ($P = 0.2357$) and AST ($P = 0.4356$) were not.

The most common grade 3+ adverse events (affecting $\geq 5\%$ of patients) were elevated AST (71%), elevated ALT (58%), neutropenia (50%), leukopenia (21%), lymphopenia (17%), infection (12%), abdominal pain (8%), hypokalemia (8%), hyponatremia (8%), hypophosphatemia (8%), and thrombocytopenia (8%).

Five patients had a total of 5 serious adverse events (SAEs), all of whom recovered. One patient had a grade 1 fever without neutropenia (possibly related), 1 had grade 3 ileus (not related), 1 had a grade 2 wound infection (possibly related), and 1 had a grade 1 intraoperative hemorrhage (not related) and a grade 3 intraoperative hemorrhage (not related). There were no study related deaths.

The CT, MR, and PET imaging features observed after LTLD plus RFA were subjectively characterized in the months following therapy (Figures 2–3). Typical features included an increase in the thermal lesion dimensions (as measured on contrast enhanced CT) from immediately post procedure compared with ~28 day imaging (Figure 3). Furthermore, in the weeks and even early months following treatment, an enhancing but smooth rim was seen on contrast enhanced CT and dynamic contrast enhanced MRI in the tissue just outside the devascularized treatment zone, at the thermal lesion margin. PET scans also showed hypermetabolic activity in the same region. This enhancing rim had a thickness greater than what is normally expected following RFA alone, but the study was not randomized and was without prospective non-drug control groups. The enhancing hypermetabolic rim regressed in the weeks to months after RFA, and remained benign-appearing on longer term imaging follow up using standard criteria (7) (Figure 3).

Discussion

RFA for limited volume focal hepatic malignancy has emerged as a safe, and effective local option for certain patients with isolated, or liver dominant disease [19–23]. Failures are often due to inability to heat tumor cells to lethal temperatures at the margin of the thermal lesion [14]. Therefore, RFA efficacy decreases as tumor size increases, especially above 3 cm [23–25]. LTLD is a heat sensitive formulation of liposomal doxorubicin that has been engineered to release doxorubicin at temperatures $> 39.5^{\circ}\text{C}$ [26]. In order to minimize these RFA treatment failures and to decrease potential toxicities of systemic chemotherapies, RFA was combined with LTLD to leverage the strengths of a drug and device combination. The combination makes use of the observation that a zone of tissue beyond the ablation zone maintains a temperature $> 39.5^{\circ}\text{C}$ and therefore would be susceptible to drug deposition [14]. This targeted drug deposition could therefore increase the effective treatment margin.

Ablation with LTLD may be a more rational combination than with a Stealth liposome by selectively releasing the drug at lower temperatures ($> 39.5^{\circ}\text{C}$) than Stealth liposomes, thus increasing the thermal margin where recurrence most often occurs [11, 27–33]. Preclinical studies have found that, at temperatures $\geq 39.5^{\circ}\text{C}$, LTLD yielded doxorubicin tumor concentrations up to 15-fold greater than the same dose of free doxorubicin. Importantly, additional preclinical studies comparing LTLD to Stealth liposomes demonstrated that LTLD combined with mild hyperthermia produced a longer growth delay and resulted in 11 of 11 complete regressions lasting up to 60 days post-treatment [26, 34]. Other emerging hyperthermia/ablation technologies, such as high intensity focused ultrasound, demonstrated a greater drug accumulation and growth delay when combined with LTLD over Stealth liposomes [35].

The observed DLT of neutropenia suggests systemic exposure to non-entrapped drug, especially given the dose dependency of neutropenia, leukopenia, and alopecia. The grade 3 neutropenia was transient and not associated with any neutropenic sepsis. The overall toxicity profile appears to be similar to doxorubicin alone.

The simultaneous delivery of heat and drug is based on preclinical models that suggested concurrent therapy maximizes drug accumulation [36]. A simple approach of initiating RFA halfway into a 30 minute IV infusion of LTLD captured 51% of the $AUC_{0-\infty}$ with RFA current on and 90% of the $AUC_{0-\infty}$ within the overall RFA time. This represents a large fraction of the $AUC_{0-\infty}$ that may be taken advantage of by the combination therapy. However, this approach does require placement of RFA needle in a prescribed time, and could have throughput implications. The steroid premedication regimen was designed based upon historical clinical and preclinical pretreatment for some liposomes, although it is unclear whether this length premedication is required.

The imaging features of LTLD treated lesions were similar to standard RFA with several important exceptions. An enhancing rim may be seen on post-RFA CT or MR images, but can appear thicker than usually seen following successful RFA and should not be confused with active tumor, especially if smooth and in the early weeks to months following RFA plus LTLD (Figures 2–3). PET activity in benign tissue may likewise also persist at the margin of treatment. These imaging features may be due to drug effect on factors such as local inflammation, wound healing, or delayed cell death in the thermal margin following this combination therapy as this is the site of most likely drug delivery [14]. The size of devascularized thermal lesions for 11 percutaneous patients were followed over time and noted to be more stable, and had larger volumes (Figure 3) than normally observed following RFA without drug. This was especially apparent in the first 4 weeks post-treatment.

A thermally deployed liposomal nanoparticle with doxorubicin is combined with thermal ablation in a drug plus device approach designed to enhance the treatment volume, and potentially improve efficacy or expand indications. A randomized phase III 600 patient global trial for hepatocellular carcinoma is underway to evaluate efficacy of this drug / device combination compared to thermal ablation alone. [37]. LTLD can be safely administered systemically in combination with hepatic RFA at a dose of 50 mg/m². Future work will examine alternative settings where this locally released drug could address a clinical problem, such as combining LTLD with MRI thermometry-guided high intensity focused ultrasound.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
 Plasma pharmacokinetics for the MTD cohort (50mg/m²) with superimposed median RFA time, showing times that the AUC was exposed to RFA.

Figure 2.

Sequential enhanced CT scans in a patient with metastatic breast carcinoma to the liver treated with RFA with IV LTLD. Pre-treatment (a), 10 weeks (b), and 12 months (c) post-treatment imaging demonstrates an enhancing thick rim at 10 weeks, which simulates residual tumor. This has the imaging appearance of benign tissue at 1 year post treatment. Although speculative, this early enhancing region is in the expected location of drug effect, but could be otherwise misinterpreted as tumor.

Figure 3.

Enhanced CT scans pre-treatment (a, arrow), 3 days (b), and 20 weeks (c), post treatment of a 49 year old female with adrenal cortical carcinoma metastases to the liver successfully treated with RFA plus simultaneous IV LTLD. Post treatment devascularized zone initially suggests incomplete ablation because the treatment zone is smaller than the tumor, but later proves successful. Whereas devascularized RFA zones typically shrink in the weeks and months following RFA alone, the RFA with LTLD zone grows in the months following treatment, suggestive of augmentation by chemotherapy.

Dose Limiting Toxicity Definitions*

Hematologic	Grade 4 thrombocytopenia
	Febrile neutropenia
	Grade 4 neutropenia > 5 days duration without growth factor support
Non-Hematologic	Any Grade 3 toxicity except:
	Vomiting only if $\geq$ Grade 3 despite the use of antiemetics
	Lab abnormalities with a causal relationship to the procedure and resolved within 72 hours of treatment
	Elevated liver functions studies that resolved to < Grade 3 within 8 days of treatment
	Grade 3 mucositis (only Grade 4 considered DLT)
Cardiac	20% reduction in left ventricular ejection fraction
Other	Events clearly unrelated to ThermoDox as assessed by the Principal Investigator were NOT considered DLTs

* NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 were employed.

Table 2**Patient and Treatment Characteristics**

Characteristic	Data (%)
No. of Patients	24 (100)
Sex	
Male	17(71)
Female	7 (29)
Age, years	
Median	58.5
Range	33–84
Baseline ECOG PS	
0	21 (87)
1	3 (13)
Histologies	
Hepatocellular carcinoma	9 (38)
Adenocarcinoma	7 (29)
Adrenal cortical carcinoma	4 (17)
Carcinoma, undifferentiated type	2 (8)
Clear cell carcinoma	1 (4)
Squamous cell carcinoma	1 (4)
Prior Therapy	
Surgery	20 (83)
Radiation	15 (62)
Chemotherapy	14 (58)
Duration of Disease, months	
Median	30.8
Range	1.9–112.7
No. Lesions Treated	
1	15 (62)
2	9 (38)
Treatment Method	
Open surgical	7 (29)
Laparoscopic	1 (4)
Percutaneous	16 (67)
Number RFA Cycles	108
Electrode Type	
Single	18 (17)
Triple	75 (69)
Triple switch	15 (14)
Tip Length (mm)	
20	27 (25)
25	53 (49)

Characteristic	Data (%)
30	14 (13)
40	14 (13)
Electrode Length (cm)	
10	16 (15)
15	55 (51)
20	6 (6)
25	30 (28)
Unknown	1(1)

Most Frequent Drug-Related Adverse Events (all grades) Affecting ≥ 5% of Patients by Dose Group													
Dose Group													
		20 (n=3)		30 (n=6)		40 (n=6)		50 (n=6)		60 (n=3)		Overall (n=24)	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Neutropenia			1	17	4	67	5	83	2	67	12	50	
Anemia	2	67	2	33	3	50	2	33			9	38	
Leukopenia			1	17	1	17	4	67	2	67	8	33	
Pyrexia	1	33	1	17					1	17	3	12	
Thrombocytopenia					1	17	2	33			3	12	
Lymphopenia					2	33					2	8	
Fatigue							1		1		2	8	
Alopecia			4	67	4	67	5	83	3	100	16	67	