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Phase II trial of combination *nab*-paclitaxel, carboplatin and gemcitabine in first line therapy of advanced urothelial carcinoma

Ajjai Alva,

University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

Stephanie Daignault,

University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

David C. Smith, and

University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

Maha Hussain

University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

Summary

Background—Paclitaxel has significant single agent activity in urothelial cancer. The 130 nm albumin bound paclitaxel (*nab*-paclitaxel, ABI-007) delivers more paclitaxel to tumor than conventional paclitaxel without cremophor related toxicities. We assessed the efficacy of *nab*-paclitaxel in combination with carboplatin and gemcitabine as first line therapy in advanced urothelial cancer.

Methods—Eligible patients had histologically confirmed metastatic, locally recurrent or advanced pure or mixed urothelial cancer, ECOG performance status of 0–2, no prior chemotherapy for current disease stage and no taxane for 1 year. Therapy consisted of *nab*-paclitaxel at 220 mg/m² intravenously with optional dose escalation to 260 mg/m² for subsequent cycles, with carboplatin AUC 5 on day 1 and gemcitabine at 800 mg/m² on days 1 and 8 in 21-day cycles. Dose modifications in all three drugs to –1 and –2 levels were allowed for toxicity. Primary endpoint was overall response rate by RECIST 1.0. Secondary endpoints were safety, progression free and overall survival. Using a two-stage design, 32 patients were planned to be enrolled.

ajjai@med.umich.edu.

Conflict of interest The authors declare that they have no conflict of interest.

Results—Due to poor accrual only 16 patients were enrolled. Thirteen patients had metastatic disease, 3 were women, and median age was 73.9 years (range 51.3–83). ECOG PS was 0 in 4 (25.0 %) and 1 in 11 (68.8 %) patients. Creatinine clearance by Cockcroft-Gault formula was less than 60 in 43 % of patients and 50 % of patients had visceral disease at baseline. The regimen was associated with severe toxicity, mainly cytopenias. Adverse events required removal of 11 patients (68.8 %) from study. Seven patients (43.7 %) missed 1 dose due to toxicity and 7 patients were reduced to –2 dose level. Nine (56.4 %) grade 3 neutropenia and thrombocytopenia each but only 1 episode of febrile neutropenia (6.3 %) was reported. Grade 3 anemia was noted in 6 patients (37.5 %). Grade 2 neuropathy was seen in 12.5 % but no grade 3 neuropathy was observed. One patient had confirmed PR (6.7 %; 95 % CI, 0–32 %) and 2 (13.3 %) had unconfirmed PR. Six other patients (40 %) had SD. Due to censoring at study exit due to adverse events before true progression, median PFS was 11.2 months (95 % CI, 2.0–11.2 m). Median overall survival was 13.1 months (95 % CI, 9.8–19.6 m).

Conclusions—The combination of *nab*-paclitaxel, carboplatin and gemcitabine was poorly tolerated in this high risk patient population at these doses and schedule. Other *nab*-paclitaxel based combinations should be explored in first line therapy of advanced urothelial cancer.

Keywords

Nano-particle albumin bound paclitaxel; Urothelial cancer; Chemotherapy

Introduction

Advanced urothelial cancer carries a poor prognosis with median survival of 13–15 months in randomized phase III trials of patients treated with first-line cisplatin-based multi-drug chemotherapy regimens. The poor survival outcomes are particularly disappointing given reasonable response rates of around 45–50 % [1, 2]. Moreover, cisplatin based regimens are associated with substantial toxicities including nephrotoxicity, ototoxicity, neuropathy and treatment related mortality of 1–3 %. Additionally, a significant percentage of urothelial cancer patients are not eligible for cisplatin due to comorbidities [3, 4]. No standard therapy has been defined in such patients but various carboplatin-based doublet and triplet regimens are routinely used in clinical practice with comparable efficacy amongst them [5–13]. The median overall survival for cisplatin ineligible patients is only 8–9 months. Therefore development of more effective therapy for cisplatin-unfit patients with advanced urothelial cancer is a critical unmet need in oncology.

Paclitaxel has one of the highest single agent activities in this disease with an overall response rate (ORR) of 42 % and a complete response (CR) rate of 20.1 % [14]. Based on this promising activity of paclitaxel and that of gemcitabine, our group investigated the combination carboplatin-paclitaxel-gemcitabine in a two institution phase II trial of 49 patients with locally advanced and metastatic urothelial cancer [15]. Patients were treated with paclitaxel at 200 mg/m² on day 1, carboplatin at target area under the curve = 5 on day 1, and gemcitabine at 800 mg/m² on days 1 and 8 in 21-day cycles. Patients received a median of 6 cycles (range: 1–15 cycles). Therapy was well tolerated with myelosuppression being the most common toxicity including grade 3 neutropenia in 17 patients (34.7 %), grade 4 neutropenia in 19 patients (38.8 %), grade 3 thrombocytopenia in 15 patients

(30.6 %), grade 4 thrombocytopenia in 6 patients (12.2 %), grade 3 anemia in 10 patients (20.4 %) and grade 4 anemia in 2 patients (40.8 %). An overall response rate of 68 % was noted with a complete response rate of 32 % and median survival of 14.7 months. A subsequent study of the combination yielded lower response rates of 43 % ORR including 12 % [16]. Regardless, paclitaxel remains one of the most effective single chemotherapeutic agents in urothelial cancer and investigation of novel taxanes continues to be of significant interest in this disease.

***nab*-paclitaxel**

nab-Paclitaxel (ABI-007 or abraxane) is a novel albumin-bound paclitaxel combining a 130 nm protein (albumin) with a chemotherapeutic agent (paclitaxel). It has been suggested that a protein specifically secreted by the tumor SPARC (Secreted Protein Acid Rich in Cysteine) and another protein caveolin-1 are involved in uptake of *nab*-Paclitaxel into the tumor [17]. In urothelial carcinoma, higher expression of caveolin-1 has been shown to correlate with higher tumor grade and increased expression of SPARC has been shown to correlate with grade, stage, and prognosis suggesting a role for SPARC and caveolin-1 in tumor progression [18–20].

A Phase III trial in patients with metastatic breast cancer compared *nab*-paclitaxel at 260 mg/m² to conventional paclitaxel 175 mg/m² given every 3 weeks [21]. The overall response rate was significantly higher for *nab*-paclitaxel than for paclitaxel (33 % v 19 % respectively; $P=0.001$). Median time to progression was also significantly longer with *nab*-paclitaxel than with paclitaxel (23.0 v 16.9 weeks, respectively; hazard ratio [HR]=0.75; $P=0.006$). There was a trend towards greater median survival in patients treated with *nab*-paclitaxel (65.0 v 55.7 weeks, respectively; $P=0.374$). On the basis of the known single agent activity of paclitaxel in urothelial cancer, the activity of combination paclitaxel-carboplatin-gemcitabine and the results from trials in breast cancer demonstrating superior clinical activity of *nab*-paclitaxel over paclitaxel accompanied by a more favorable toxicity profile, we initiated a single institution single arm phase II trial evaluating the efficacy and safety of the combination of *nab*-paclitaxel, carboplatin, and gemcitabine in patients with advanced urothelial cancer. We also had an ongoing phase II neoadjuvant study in urothelial cancer (UMCC 2007.061) at that time with weekly *nab*-paclitaxel at 100 mg/ m² on days 1 and 8, gemcitabine at 1,000 mg/ m² on days 1 and 8 and carboplatin at AUC of 5 on day 1 given every 21 days.

Patients and methods

Eligibility

Adult patients were eligible for the study if they had a histologic or cytologic diagnosis of urothelial cancer/transitional cell cancer (either pure or mixed) that was metastatic or locally recurrent or locally advanced with measurable disease. An Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, life expectancy of at least 12 weeks and adequate organ and hematologic function (absolute neutrophil count 1,500/uL, platelets 100,000/uL, serum creatinine 2 mg/dL irrespective of estimated or measured GFR, normal bilirubin and aspartate aminotransferase or alanine aminotransferase $2.5 \times$ upper

limits of normal) were required. Patients who had prior systemic chemotherapy for the current stage of disease or prior treatment with *nab*-paclitaxel or other taxanes were excluded with the exception of prior treatment with taxanes in the neo-adjuvant or adjuvant setting more than 1 year prior. Pre-existing neuropathy of grade 2 or greater severity was an exclusion criterion. All patients with reproductive potential had to agree to use effective contraception during the period of therapy. All women of child-bearing potential had to have a negative serum pregnancy test. All patients signed an informed consent approved by the University of Michigan Institutional Review Board. All patients were registered with the University of Michigan Cancer Center Clinical Trials Office.

Treatment plan

The neoadjuvant study revealed significant marrow suppression and required dose reductions in the first three patients enrolled. The neoadjuvant study was subsequently revised to *nab*-paclitaxel dosed at 260 mg/m² on day1 followed by carboplatin at target AUC=5 on day 1 and gemcitabine at 800 mg/m² on days 1 and 8 in a 21-day cycle. Therefore, we initiated the advanced bladder cancer trial with *nab*-paclitaxel at 260 mg/m² as in the revised neo-adjuvant trial. Fifteen patients received at least 1 dose of *nab*-paclitaxel at 260 mg/m². However, significant bone marrow suppression was encountered and therefore the protocol was amended to reduce the starting dose of *nab*-paclitaxel to 220 mg/m² with the option of a dose escalation in patients who tolerated the starting dose.

After the protocol revision, *nab*-paclitaxel was administered intravenously over 30 min at a dose of 220 mg/m² with possible dose reduction to 180 mg/m² or dose escalation to 260 mg/m² for subsequent cycles. Carboplatin was given intravenously at AUC of 5 (dose reductions to AUC of 4 and 3 were permitted) over 15 min and Gemcitabine intravenously at a starting dose of 800 mg/m² over 30 min (–2 dose level: 600 mg/m²). Day 8 therapy with gemcitabine was allowed if ANC ≥ 1,000 and platelets > 75,000. Carboplatin dose was calculated using the well-established Calvert formula (Carboplatin dose (mg) = target AUC × [GFR + 25]) and adjusted ideal body weight was used for patients with BMI > 30 kg/m² in the estimation of creatinine clearance [22]. Routine prophylactic pre-medications for *nab*-paclitaxel hypersensitivity were not given. Anti-emetics were administered per institutional guidelines and modified per investigator discretion. G-CSF was administered in accordance with the American Society of Clinical Oncology (ASCO) guidelines.

The revised protocol called for interruption of protocol therapy and initiation of antibiotics (ciprofloxacin or amoxicillin/clavulanate) for any fever greater than 38.5 Celsius (101.3 F) regardless of ANC followed by a dose reduction on therapy resumption at resolution of fever and recovery of blood counts. The CTCAE (NCI Common Terminology Criteria for Adverse Events) version 3.0 was used. *nab*-Paclitaxel was held for grade 2 or 3 sensory neuropathy until improvement to grade 0 or 1 and resumed at one dose lower. Liver function tests were required to meet study entry criteria at the beginning of each cycle. Other grade 2 or lower non-hematological toxicities were managed symptomatically when possible without dose reduction. Treatment was held for grade 3 or 4 non-hematological toxicity until resolution to grade 1 or 0 and resumed if medically appropriate at the next lower dose level.

Duration of therapy and monitoring

At baseline, patients underwent axial imaging of the chest, abdomen and pelvis and a whole body nuclear medicine bone scan. Patients continued on therapy for a maximum of 6 cycles, objective or symptomatic disease progression, withdrawal of consent, 2 cycles beyond complete response or deterioration in general medical condition that precluded further protocol therapy. All study patients were seen on the first day of each cycle for physical examination, history and estimation of ECOG Performance Status. A complete blood count with differential was performed weekly and a comprehensive metabolic panel was drawn on the first day of each cycle. Imaging studies were repeated every 3 cycles except bone scan which was only repeated if known bone metastases were present or symptoms or signs suggested their presence. After protocol specified chemotherapy, survival data was collected every 6 months until death.

End points and statistical design

The primary objective of the study was to determine the overall response rate (Complete response + Partial response) of the combination of *nab*-paclitaxel, carboplatin, and gemcitabine in patients with advanced urothelial carcinoma. The primary endpoint was overall response rate (CR+PR) as assessed by RECIST 1.0 criteria, to be reported with a 95 % confidence interval. The secondary objectives were to assess the safety and tolerability of *nab*-paclitaxel, carboplatin, and gemcitabine combination therapy by CTCAE version 3.0 criteria, progression free and overall survival and the association of SPARC (a molecular marker) with response in tumor specimens. The association between SPARC and response was not explored due to poor accrual. Response and progression were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

A response rate of 50 % with this drug combination was considered uninteresting, while a response rate of 75 % would be clinically interesting and meriting further study. A two-stage MiniMax design was utilized. With 5 % type I error and 90 % power the first stage was designed to enroll 21 patients, of which 13 or more responses were needed for continuation onto the second stage. The second stage was designed to accrue 11 additional patients for a total of 32 patients, of which 21 or more would need to respond to reject the null hypothesis. The expected sample size if the null hypothesis value for response, 50 %, was true was 23.1 patients. If the true response rate was 50 %, then we would have 80.1 % probability of terminating the trial after the first stage and 5.6 % of stopping early if the true response was 75 %. A patient was deemed evaluable for response if they complete one cycle. Non-evaluable patients were to be replaced in the trial for the purpose of evaluating the primary endpoint. There was a minimum of 24 months of follow-up planned on each subject.

The primary endpoint was a tabulated frequency of the overall response rate (CR+PR) and is presented as the number of patients and the frequency. Tabulations were also calculated for adverse events. Progression-free survival and overall survival were analyzed using the Kaplan-Meier method and the medians and associated 95 % confidence intervals are reported.

Results

Baseline patient characteristics

The baseline characteristics of enrolled patients were typical of the advanced bladder cancer patient population (Table 1). Nearly half the patients (43.8 %) had an estimated creatinine clearance of less than 60 ml/min by Cockcroft Gault formula and predominantly male patients. Most patients (11/16) had an ECOG performance status of 1 while one patient was of ECOG PS of 2. Visceral disease including liver, lungs or bone involvement was noted in 50 % of trial patients at baseline. The Memorial Sloan-Kettering Cancer Center (MSKCC) risk-score model which is based on performance status and presence or absence of visceral disease was 2 in 6 patients and 1 in 4 other patients [23]. Six patients had received chemotherapy prior (4 as neoadjuvant; 2 others for locally advanced disease). In 2 of the patients treated with neoadjuvant chemotherapy, prior chemotherapy was with carboplatin/gemcitabine/paclitaxel, completed 14 months and 27 months earlier. Two others had received neoadjuvant cisplatin based regimens (cisplatin/gemcitabine and MVAC), completed 24 months and 4 months prior.

Treatment related toxicity

Fifteen patients started protocol therapy at the original dose of 260 mg/m² of *nab*-paclitaxel. After the protocol revision, patients still on study were treated with a reduced dose of 220 mg/m² of *nab*-paclitaxel. One other patient started protocol therapy at 220 mg/m² after the protocol revision. Altogether, 12 patients received the dose of 220 mg/m² of *nab*-paclitaxel. The protocol specified therapy was associated with profound and early myelosuppression (Table 2). There were three grade 3 and two grade 4 neutropenia events noted in the very first cycle of therapy. In addition there was one each of grade 3 and grade 4 thrombocytopenia encountered in the first cycle. Seven patients (43.7 %) missed 1 dose due to toxicity and 7 patients were reduced to 180 mg/m² level of *nab*-paclitaxel. In all, nine (56.3 %) grade 3 neutropenia and thrombocytopenia each and 1 episode of febrile neutropenia (6.3 %) were reported. Despite the incidence of severe neutropenia, there was only 1 occurrence of neutropenic fever. Gr 3 anemia was noted in 6 patients (37.5 %). Grade 2 neuropathy was seen in 2 patients (12.5 %) but no grade 3 or 4 neuropathy was seen. No patient had a dose escalation of *nab*-paclitaxel above the starting dose.

Efficacy and survival

The efficacy results from this study are complicated by the high frequency of censoring due to patients withdrawing from protocol early, as 11 patients were removed from protocol due to toxicity of which 7 began other therapies before progression was documented and 1 patient withdrew consent (Fig. 1) The overall response rate included one patient (6.3 % 95 % CI [0.2–32 %]) who had a confirmed partial response among the 15 evaluable patients. Additionally, two patients (13.3 %) had unconfirmed PR. The median progression-free-survival (PFS) was 11.2 months (95 % CI, 2.0–11.2 m) (Fig. 2). Median overall survival was 13.1 months (95 % CI, 9.8–19.6 m) (Fig. 2). The number of treatment cycles ranged from 1 to 8 with a median of 3. Median PFS follow-up was 5.1 months (range 1–11.2) and median survival follow-up was 13.1 months (range: 2–21).

Discussion

Development of a non-cisplatin based chemotherapy regimen for bladder cancer has been a goal in oncology for decades for several obvious reasons. Specifically, maximizing antitumor effect beyond that observed with current agents while avoiding cisplatin-related adverse effects that prohibit cisplatin therapy in a significant percentage of urothelial cancer patients has been a key objective. The incorporation of a novel, possibly more effective formulation of paclitaxel to carboplatin- gemcitabine was hypothesized to have the potential to achieve that goal. The *nab*-paclitaxel, carboplatin and gemcitabine regimen however was excessively toxic at the doses used in this study with cytopenias noted even after 1 week of therapy requiring a protocol modification to lower the dose of *nab*-paclitaxel. In addition, aggressive and early initiation of antibiotics in response to fever regardless of blood counts was instituted and incorporated into the amended protocol. However, these changes did not appear to alter the toxicity profile. The unexpected and excessive toxicity prompted premature discontinuation or withdrawal of 11 patients. The high withdrawal rate rendered pointless any attempt at assessment of the regimen's efficacy. The original study protocol called for analysis of tumor specimens when available for SPARC expression to determine the association of SPARC protein with response. Due to the small number of tumor samples and conflicting data reported in head and neck cancer samples, the correlative aim of the trial was abandoned and no analysis of SPARC expression in tumor samples was performed.

The hematologic toxicity encountered with the *nab*-paclitaxel, carboplatin and gemcitabine combination in advanced urothelial cancer patients in this trial was more severe than our experience with the same combination in a neoadjuvant trial conducted concurrently at our institution where all but 3 of the 26 patients received all 3 cycles intended with similar doses [24]. However, the neoadjuvant population with bladder cancer is a much more robust group in terms of the ability to tolerate cytotoxic chemotherapy than advanced bladder cancer patients who have a greater burden of disease, inferior performance status and poor renal function. An alternative schedule of therapy administration is another modification to consider. A weekly dosing of *nab*-paclitaxel at 100 mg/m² and carboplatin at AUC of 2 was investigated in metastatic melanoma and appeared to be reasonably well tolerated [25]. The common grade 3 or 4 toxicities did include neutropenia and thrombocytopenia. A second look at a weekly *nab*-paclitaxel schedule in combination with carboplatin may be warranted as the combination has been reported to be well tolerated in non-small cell lung cancer, including in elderly patients [26, 27]. *nab*-Paclitaxel could still be investigated in first line therapy potentially in both cisplatin eligible and ineligible patients with advanced urothelial cancer in combination with cisplatin, carboplatin or gemcitabine based on the clinical context.

In retrospect, a phase I trial for the combination specifically in advanced urothelial cancer could have allowed a more appropriate *nab*-paclitaxel dose for the combination due to unique patient characteristics of this population which are different from even the neoadjuvant setting. *nab*-paclitaxel has also been studied as a single agent in a multicenter Canadian trial in patients with advanced urothelial cancer who had progressed on a first line platinum containing regimen for metastatic disease or within 12 months of perioperative chemotherapy [28]. Patients received *nab*-paclitaxel at a dose of 260 mg/m² every 3 week.

The median number of cycles was six. Among the 47 evaluable patients, 13 patients had a response (1 complete and 12 partial) for a response rate of 27.7 % (95 % CI 17.3–44.4). Contrary to our experience with *nab*-paclitaxel based combination therapy, single agent *nab*-paclitaxel appears to have a reasonable tolerability profile with promising efficacy. A randomized phase 3 trial is being planned. Cytopenias were not prominent with single agent *nab*-paclitaxel leading us to conclude that the combination with carboplatin and gemcitabine likely resulted in the observed toxicity in our study.

In the randomized trial of carboplatin-gemcitabine (GCa) versus methotrexate-carboplatin-vinblastine (M-CAVI) [13], patients with impaired renal function and/or poor performance status had markedly inferior responses on both arms compared to response rates in the study cohort as a whole [13]. For example, the response rates for patients with GFR <60 mL/min and PS of 2 was only 20–26 % compared to 30–42 % for the overall trial. The poor response was accompanied by a severe acute toxicity rate of 25–26 %. In our trial, 7 (43.7 %) had a GFR of <60 mL/min but only one patient had PS of 2. Only six patients had received any prior chemotherapy including 4 who had had neoadjuvant chemotherapy. Of these 4, two had been treated with carboplatin and paclitaxel and 2 others had received cisplatin based regimens. Therefore, the study population characteristics do not entirely explain the severe toxicity noted in this trial.

A clear advantage of *nab*-paclitaxel versus paclitaxel was the lack of hypersensitivity reactions consistent with the reported *nab*-paclitaxel experience. However, the experience in our trial was limited as the median number of cycles was only 3 (range 1–8). In summary, the combination of *nab*-paclitaxel given once every 3 weeks in combination with carboplatin and gemcitabine for patients with advanced bladder cancer was poorly tolerated with profound myelosuppression encountered and cannot be recommended for clinical use at the current strengths or schedule.

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Fig. 1.
Consolidated standards of reporting trials diagram

Fig. 2.
Overall survival (OS) and progression-free-survival (PFS) of study patients

Table 1**Baseline patient demographics**

Variable	Value (%)
Age (years)	
Median	73.9
Range	51.3–83
Gender	
Male	13 (81.3)
Female	3 (18.8)
Histology	
Pure urothelial (including 4 nested, 2 micropapillary variants)	13 (81.3)
Mixed urothelial with squamous	2 (12.5)
Mixed urothelial with adenocarcinoma	1 (6.3)
Primary site	
Bladder	13 (81.3)
Ureter/renal pelvis	3 (18.8)
Disease status	
Metastatic	13 (81.3)
Locally advanced or recurrent unresectable	3 (18.8)
GFR (Cockcroft-Gault, mL/min)	
60	9 (56.3)
<60	7 (43.8)
ECOG performance status	
0	4 (25)
1	11 (68.8)
2	1 (6.3)
Visceral disease in the 13 metastatic patients	8 (50)
Bajorin score in the 13 metastatic patients	
0	3 (18.8)
1	4 (25)
2	6 (37.5)
Prior chemotherapy	6 (37.5)
Neoadjuvant	
Carboplatin/gemcitabine/paclitaxel	2 (12.5)
Cisplatin/gemcitabine	1 (6.3)
Methotrexate/vinblastine/doxorubicin/cisplatin	1 (6.3)
For locally advanced cancer	
Cisplatin/gemcitabine/erbitux (as part of a trial)	1 (6.3)
Cisplatin and capecitabine	1 (6.3)

Table 2

Grade 3 and 4 toxicity during protocol chemotherapy for all 16 patients

Adverse event	Grade 3 %	Grade 4 %
Thrombocytopenia	43.75 %	12.5 %
Leukopenia	37.5 %	25 %
Lymphocytopenia	31.3 %	6.3 %
Anemia	31.3 %	6.3 %
Neutropenia	25 %	31.3 %
Pain	18.8 %	6.3 %
Fatigue	12.5 %	–
Nausea	12.5 %	–
Infection	6.3 %	6.3 %
Mucositis	6.3 %	6.3 %
Arthritis	–	6.3 %
Hemarthrosis	6.3 %	–
DVT	6.3 %	–
Diarrhea	6.3 %	–
Vomiting	6.3 %	–
Gastrointestinal hemorrhage	6.3 %	–
AST abnormalities	6.3 %	–
ALT abnormalities	6.3 %	–