厚生労働科学研究費補助金
がん臨床研究事業

進行卵巣がんの集学的治療に関する研究

（H16ーがん臨床ーー般ー035）

平成16年度～18年度　総合研究報告書

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目　　次

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主任研究者　吉川　裕之　筑波大学大学院人間総合科学研究科　教授

研究要旨

卵巣がん、卵管がん、腹膜がんを対象として、化学療法先行の治療法を標準治療の手術先行の治療法と比較するランダム化比較試験を行う前段階として feasibility study（JCOG 0206）を行い、平成 17 年 3 月に行われた中間解析の結果を同年 5 月に ASCO において発表した。その結果から第 III 相試験を行うことの妥当性がされた。最終解析は平成19年3月である。

化学療法先行治療と手術先行の標準治療とのランダム化比較試験（JCOG 0602）は、非劣性試験で、Primary endpoint は生存期間である。本年度は第 III 相試験の実施計画書作成を行い、最終審査を経て、平成 18 年 11 月に JCOG 0602 として手術先行治療との第 III 相試験（非劣性試験）の登録を開始した。

予定登録数：各群 150 例、両群計 300 例で、症例集積期：3 年。追跡期間：登録終了後 5 年。総研究期間：8 年。

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A．研究目的

Feasibility study (JCOG 0206)

Feasibility study の目的は、卵巣がん、卵管がん、腹膜がんを対象として、化学療法先行の治療法を標準治療の手術先行の治療法と比較するランダム化比較試験を行う前段階として、化学療法先行の治療法が第 III 相試験の試験治療として適切かどうかを判断し、かつ第

III 相試験を行う場合、試験治療群において診断的腹腔鏡が必須かどうかを決定することである。また、その結果を踏まえ、第 III 相試験を開始することである。

ランダム化比較試験(JCOG 0602)

III、IV 期の卵巣がん、卵管がん、腹膜がんに対して、手術の前後に 4 コースずつ計 8 コースの化学療法を行う「化学療法先行治療」が、現在の標準治療である、手術後に計 8 コースの化学療法を行う「手術先行治療」よりも有用であるかどうかをランダム化比較試験にて検証する。

Primary endpoint：全生存期間。Secondary endpoints：完全腫瘍消失割合、無増悪生存期間、奏効割合(B 群のみ)、有害事象、手術侵襲指標(開腹手術回数、総開腹手術時間、出血量、総輸血量、総血漿製剤使用量)。

B．研究方法

JCOG 0206

適格規準は、①画像所見で卵巣、卵管、腹膜がん III/IV 期、②術前細胞診が上記に一致。③初回腫瘍縮小手術の対象と成りうる。④CA125 > 200 U/ml かつ CEA < 20 ng/ml。⑤測定可能病変を有する。⑥年齢 20-75 才。⑦ PS 0-3。⑧諸臓器機能が保たれている。

登録後、診断的腹腔鏡を行い、悪性であること、原発が上記臓器であること、進行期が III/IV 期であること、組織型を確認する。その後 1 週以内に化学療法 (TXL175 mg/m^2 +CBDCA AUC6 を手術前後に 4 コース、計 8 コース) を開始する。PD 例を除き、4 コース後に ICS (腫瘍縮小手術) を行い、その後 4 コースの化学療法を行い、Primary endpoint である完全腫瘍消失[CT または MRI で病変が消失し,CA125<20]率 (閾値割合 20%、期待割合 40%) について評価する。登録例が診断的腹腔鏡後にて適格 (正診) とされる割合 (90%以上) も secondary endpoint として検討する。目標登録数は 56 例で、登録期間は 1 年である。

JCOG 0602

研究形式は多施設共同の第 III 相ランダム化比較試験 (非劣性試験)。対象症例は、開腹以外の手段で組織学的または細胞学的に診断され、CT/MRI で進行期分類された上皮性卵巣がん、卵管がん、腹膜がん III/IV 期の初回治療例で、20-75 才、CA125>200 IU/ml, CEA<20 ng/ml、ECOG PS 0-3、適当な骨髄・肝・腎機能が保持され、初回腫瘍縮小手術の対象となりうる症例とする。

症例登録とランダム割付は、データセンターでの中央登録方式をとる。電話または FAX にて症例登録を行い、適格性の確認後、治療群の割付を受ける。ランダム化割付には、調整因子として施設、PS、臨床進行期、年齢を用いる。

解析方法としては、予定症例数の半数の登録時点と症例集積終了後にログランク検定にて両群の生存期間を比較する。予定登録数：各群 150 例、両群計 300 例。

症例数算定の根拠は次のとおりである。NAC 療法が標準治療に劣るかどうかは関心事項ではないため、有意水準 α=0.05 の片側検定とする。PCS の真の 3 年生存率を 25%と想定し、NAC がそれを下回る許容限界を 5%とする。NAC 療法の真の 3 年生存率が 30.3%であれば、80%の検出力で非劣性を検証することができる。

実施施設は本研究の研究者の所属施設を中心に、全国の卵巣がん治療の基幹施設 30 施設。

(倫理面への配慮)

参加患者の安全性確保については、正確な診断、有用性の高い治療等に配慮がなされており、試験参加による不利益は最小化される。また、「臨床研究に関する倫理指針」およびヘルシンキ宣言等の国際的倫理原則に従い以下を遵守する。①研究実施計画書 (プロトコール) の IRB 承認が得られた施設からしか患者登録を

行わない。②すべての患者について登録前に充分な説明と理解に基づく自発的同意を本人より文書で得る。③データの取扱い上、患者氏名等直接個人が識別できる情報を用いず、かつデータベースのセキュリティを確保し、個人情報（プライバシー）保護を厳守する。

研究の第三者的監視：本研究班により、もしくは賛同の得られた他の主任研究者と協力して、臨床試験審査委員会、効果・安全性評価委員会、監査委員会を組織し、研究開始前および研究実施中の第三者的監視を行う。

C．研究結果

予定の56例の登録が終了した。患者年齢は33-73歳（中央値 55歳）で、登録時の画像による病期はIII期42例、IV期14例（腹腔鏡前ではIII期38例、IV期18例）であった。登録時PSは0が28例、1が18例、2が7例、3が3例であった。全例で、腹水・胸水・腫瘍穿刺液のいずれかの細胞診が腺癌であった。

ICSについては非正診の3例を除く53例のうち、47例でICSが行われ、6例（PD 3例、患者拒否1例、有害事象中止2例）で施行されなかった。ICSでの完全手術(残像腫瘍なし)は、29/47(61.7%)と高率であった。

診断的腹腔鏡で確認された病期は、I期1例、2期2例、3B期4例、3C期31例、IV期18例であった。腹腔鏡時の原発臓器診断は全例適格で、生検の病理組織診断は、腺癌20例、漿液性腺癌29例、粘液性腺癌2例、類内膜腺癌5例で全例適格であった（ICS時の組織診断は、漿液性腺癌41例、粘液性腺癌1例、類内膜腺癌1例、明細胞腺癌2例、移行上皮癌1例、未分化癌1例)。診断的腹腔鏡前の臨床診断の正診割合は53/56(94.6%)で、第III試験での診断的腹腔鏡の省略が決定された。診断的腹腔鏡前でI/II期と診断されたものは3名であった（そのうち1名は直後の開腹でIII期であることが判明した。それを含めた正診割合は54/56[96.4%])。完全腫瘍消失割合は18/53（34.0%, 95%CI;21.5-48.3%)で、閾値割合 20%を下回らないことが確認された。他に途中でprotocol治療中止の4名が完全腫瘍消失を達成しており、それを含めた完全腫瘍消失割合は22/53(41.5%)であった。完全腫瘍消失割合は閾値割合を下回らないと結論され（17/53以上の条件をクリア)、第III相比較試験を行うことが決まった。

平成19年3月8日現在のJCOG 0602のIRB承認は30施設中23施設、登録は7例である。IRB承認直後の施設が多いので、今後の登録が促進されることが期待される。

D．考察

この新治療体系の確立は、治療成績を変えずにまたは向上させて、手術回数・侵襲を減少させることが期待される。化学療法先行治療に関して唯一先行しているEORTCでは、第III相試験を開始し、診断的開腹または腹腔鏡の後に手術先行群と化学療法先行群に割り付けているが、結果として手術先行群に余分な開腹または腹腔鏡を行っている。診断的腹腔鏡の省略により、化学療法先行の利点である早期治療開始をさらに早めることができ、かつ現在臨床の現場で行われる切除不能例に対する化学療法先行治療にも一致する。

卵巣がんIII/IV期に対する治療成績は3年生存率25%であり、現在の標準治療は、診断優先で治療の負担も大きく、難しい治療体系のため均てん化も遅れている。治療成績の向上、治療の低浸襲化、均てん化には新たな治療体系の確立が必要であり、化学療法先行治療の標準化を目指す本試験の実施が必要である。本研究では非劣性試験を行うが、これを立証するには3年生存率を 5%以上向上させる必要がある。我が国の卵巣がん年間死亡数は4200人以上であり、その80%以上がIII/IV期例である。生存率改善に加え、手術回数減少に加え、手術時の

PS 改善、手術縮小で合併症・輸血などの減少が期待され、患者負担減少・医療経済改善に貢献するとともに、治療が定型化しやすく、均てん化にも貢献できる。手術数の減少はがん専門病院での治療数増加にも繋がり、急増する卵巣がん症例数に対応できる体制が整う。

E．結論

卵巣がん、卵管がん、腹膜がんを対象として、化学療法先行の治療法を標準治療の手術先行の治療法と比較するランダム化比較試験を行う前段階として feasibility study を行い、その結果、第 III 相試験が feasible であることが確認され、プロトコール承認後、平成 18 年 11 月より登録が開始された。

第 III 相試験として進行中の EORTC55971 では第 II 相試験を省略したために、多くの問題が生じている。両群で診断的開腹・腹腔鏡を行うために、化学療法先行群では化学療法早期開始という利点を半減させ、手術先行群では標準治療以外のことを加えることが最大の欠点である。本試験では第 II 相試験の成果により、化学療法先行治療の特性を最大限に生かし、EORTC 試験の欠点を克服した厳密な臨床試験とすることができた。

F．研究発表

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G．知的所有権の取得状況

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

研究成果の刊行に関する一覧表

書籍：該当なし

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Cisplatin, Paclitaxel and Escalating Doses of Doxorubicin (TAP) in Advanced Ovarian Cancer: a Phase I Trial

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Background: The objectives of this phase I trial were to determine the maximum tolerated dose (MTD) and the recommended dose (RD) for phase II/III trials of doxorubicin (DOX) combined with paclitaxel (PTX) and cisplatin (CDDP) in patients with advanced ovarian cancer (AOC).
Methods: Twenty-eight patients with stage III/IV AOC received fixed doses of PTX (110 mg/m^2 over 24 h on day 1) and CDDP (75 mg/m^2 on day 2) and an escalating dose of DOX (20, 30, 40 or 50 mg/m^2 on day 1) every 3 weeks. The patients received up to six cycles of chemotherapy. At level 1, one of the original dose-limiting toxicities (DLTs), grade (G) 4 neutropenia lasting for 4 days or longer, occurred in four of six patients. The criterion for DLT was amended to 'G4 neutropenia lasting for 8 days or longer accompanied with G4 leukopenia' and four additional patients were evaluated at level 1.
Results: According to the new criteria, DLT was observed only in one of nine patients except one ineligible patient at level 1and two of six patients at level 4. G4 neutropenia and G4 leukopenia occurred in 85% and 44%, respectively, in the first course of chemotherapy. Non-hematological toxicity was generally mild or moderate. MTD was not determined at the planned dose levels. A clinical response was observed in 16 of 19 (84%) evaluable patients. Further dose escalation was not performed and RD was determined as level 4 because more than 30% of cycles required some modification of chemotherapy at level 4.
Conclusion: The combination of TAP including 50 mg/m^2 of DOX is feasible and well tolerated as first line chemotherapy in AOC, warranting further study of this regimen.

Key words: ovarian cancer – chemotherapy – doxorubicin – phase I study

INTRODUCTION

Since randomized trials have demonstrated the superiority of paclitaxel (PTX) plus cisplatin (CDDP) over cisplatin plus cyclophosphamide (CPA) in overall survival and progression-free survival (1,2) and subsequent trials demonstrated similar activity of PTX plus carboplatin (CBDCA) compared with PTX plus CDDP (3), the combination regimen of PTX plus platinum, such as CDDP or CBDCA, is considered the standard regimen for advanced ovarian cancer (AOC). The two-drug combination regimen of PTX and platinum yields a high response rate and improved survival for patients with AOC. In spite of chemotherapy development, the 5-year survival of patients with stage III/IV ovarian cancer is generally less than or around 20% (4), which is far from satisfactory. Therefore, several approaches, especially new agents or new drug combinations, are being examined in clinical studies to improve further the outcome of treatment for AOC.

Doxorubicin (DOX), an anthracycline, is known to be an active agent for ovarian cancer and was used in combination with CDDP and CPA as a standard regimen for ovarian cancer before the introduction of PTX plus platinum. The benefit of

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adding DOX to CDDP and CPA was controversial. A phase III randomized trial of CDDP plus CPA with or without DOX conducted by the Gynecological Oncology Group (GOG) (5) showed no clear benefit of DOX in the pathological complete response rate and median survival time. However, three meta-analyses demonstrated that the incorporation of DOX into the CDDP-based regimen for ovarian cancer may improve the long-term survival of AOC by 7–10% (6–8). Therefore, the value of DOX in the treatment of ovarian cancer was re-examined.

The benefit of adding DOX to the current standard regimen, PTX and platinum, should be evaluated to improve further the outcome of patients with AOC. To evaluate the safety and efficacy of this combination regimen, we conducted a phase I trial in patients with AOC for first-line chemotherapy using a combination of fixed doses of CDDP and PTX with escalating doses of DOX given every 3 weeks.

PATIENTS AND METHODS

Selection of Patients

The subjects of this study were untreated patients with stage IIIC or IV epithelial ovarian cancer. The histology of tumors included serous, mucinous, endometrioid, clear cell, mixed epithelial, undifferentiated, malignant Brenner, transitional cell and unclassified types. Patients with low potential malignancies were not included.

Other eligible criteria for entry into this study were as follows: (a) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (b) age 16–75 years; (c) adequate bone marrow function [white blood cell count (WBC) $\geq$3000/mm^3 or absolute neutrophil count (ANC) $\geq$1500/mm^3 and platelet count $\geq$100 000/mm^3], adequate hepatic function [total serum bilirubin $\leq$1.5 mg/dl and serum aspartate aminotransferase (AST) $\leq$2.5 times the upper limit of normal], adequate renal function (serum creatinine $\leq$1.5 mg/dl and creatinine clearance $\geq$50 ml/min) and adequate cardiac function (normal or minor deviation in electrocardiogram); and (d) written informed consent. Patients were ineligible if they had (a) severe mental disorders; (b) uncontrolled hypertension; (c) history of cardiac failure, unstable angina, myocardial infarction within 6 months prior to the study; (d) liver cirrhosis; (e) diabetes mellitus, controlled with insulin; (f) history of severe hypersensitivity or hypersensitivity to drugs formulated with polyoxyethylated castor oil (Cremophor EL) as an ingredient (e.g. cyclosporine or vitamin K); (g) hepatitis B e antigen (HBeAg) or antibody against hepatitis C virus (HCV); or (h) if they were pregnant.

Treatment Plan

All patients underwent staging laparotomy and, simultaneously, maximum cytoreductive surgery. Following surgery, eligible patients were enrolled into the study. Patients received up to six cycles of chemotherapy consisting of paclitaxel (PTX), doxorubicin (DOX) and cisplatin (CDDP). DOX was administered as a 30 min intravenous (IV) infusion on day 1. PTX was administered as a 24 h continuous i.v. infusion on day 1 following DOX administration. CDDP was administered as a 2 h i.v. infusion on day 2. Chemotherapy was repeated every 21 days, assuming recovery from the toxicity of the previous cycle. Four different dose levels were tested. The dose of DOX was escalated from 20 mg/m^2 (level 1) to 50 mg/m^2 (level 4) in increments of 10 mg/m^2 in sequential cohorts and doses of PTX and CDDP were fixed at 110 and 75 mg/m^2, respectively.

A pre-medication schedule consisted of a 20 mg intravenous dexamethasone infusion 12 and 6 h before chemotherapy, 50 mg oral diphenhydramine and 50 mg intravenous ranitidine administration 30 min before chemotherapy. No primary granulocyte colony-stimulating factor (G-CSF) prophylaxis was allowed. G-CSF use was allowed only when grade 4 leukopenia (<1000/m^3) or grade 4 neutropenia (<500/m^3) lasting for 3 days or longer or grade 2 fever ($\geq$38°C) during grade 3 leukopenia (<2000/m^3) or grade 3 neutropenia (<1000/m^3) was observed.

Treatment Modification

Re-treatment was delayed until the following criteria were met. (a) WBC $\geq$2500/mm^3 and platelet count $\geq$100 000/mm^3; (b) total serum bilirubin $\leq$1.5 mg/dl, serum AST $\leq$2.5 times the upper limit of normal and serum creatinine $\leq$1.5 mg/dl; (c) more than 48 h passed after the final G-CSF use; and (d) absence of active infection. Patients were taken out of the study if the treatment interval exceeded 42 days.

For patients experiencing any of the following toxicities, the doses of all three drugs were reduced to 90% of the previous dose: (a) grade 4 leukopenia (<1000/m^3); (b) grade 2 fever ($\geq$38°C) lasting for 3 days and/or bacteremia during grade 3 leukopenia (<2000/m^3) or neutropenia (<1000/m^3); (c) grade 3 thrombocytopenia (<50 000/m^3); and (d) grade 3 or 4 non-hematological toxicities other than nausea and vomiting. Toxicities were graded according to the Japan Clinical Oncology Group (JCOG) toxicity criteria (9), based on Common Toxicity Criteria of the National Cancer Institute (NCI-CTC, 1982) to extend and supplement the criteria.

Chemotherapy was discontinued if (a) response was revealed to be no change (NC) after three cycles of chemotherapy, (b) progressive disease (PD) was observed, (c) unacceptable toxicities were observed or (d) recovery from toxicities was prolonged.

Determination of Maximum Tolerated Dose and Recommended Dose

The primary objectives of the study were to determine the maximum tolerated dose (MTD) and the recommended dose (RD) of DOX when combined with 110 mg/m^2 of PTX and 75 mg/m^2 of CDDP. Initially, six patients were sequentially enrolled into the lowest dose level. Dose-limiting toxicity

(DLT) was evaluated in the first course of chemotherapy to determine MTD and in all courses of chemotherapy to determine the RD. If none or one of the six patients experienced DLT, then the following six patients would be enrolled into the next dose level. If four or more of the six patients experienced DLT and the dose level was higher than level 1, MTD was determined as the previous dose level. If two or three of the six patients experienced DLT, then an additional six patients would be enrolled into the same dose level at other than level 4. If three or fewer of 12 patients experienced DLT, then the next six patients would be enrolled into the next dose level. If four or more of 12 patients experienced DLT, then MTD was determined as that dose level. These steps were repeated until MTD was determined. RD was determined taking into account the DLT observed in the following courses of chemotherapy.

DLT was initially defined as (a) grade 4 leukopenia ($<1000/m^3$) or grade 4 neutropenia ($<500/m^3$) lasting for 4 days or longer; (b) grade 2 fever ($\geq 38°C$) lasting for 3 days and/or bacteremia during grade 3 leukopenia ($<2000/m^3$) or neutropenia ($<1000/m^3$); (c) grade 4 thrombocytopenia ($<25\,000/m^3$); and (d) grade 3 or 4 non-hematological toxicities other than nausea and vomiting. The criteria were subsequently amended as described in the next subsection.

Amendment of Criteria for Dose-limiting Toxicity

Among six patients enrolled into dose level 1, grade 4 neutropenia lasting for 4 days or longer [criterion (a)] was observed in four patients during the first course of chemotherapy and neutrophils were not counted in one patient with grade 2 leukopenia. Therefore, the study was discontinued and the toxicities were evaluated. Grade 4 neutropenia was observed for 6–7 days in three patients and observed for 11 days in one patient, although grade 4 leukopenia was not observed. However, all six patients recovered from the toxicity and could receive the subsequent course of chemotherapy without delay. No other DLT was observed in these six patients during the first and subsequent courses. Therefore, dose level 1 was evaluated to be safe and criterion (a) was considered to be too strict. Moreover, many phase I studies for ovarian cancer adopted a criterion of 'grade 4 neutropenia lasting for 8 days or longer' (10–14). Taken together, the following amendment of criteria and study design was permitted by the Data and Safety Monitoring Committee. (1) Criterion (a) was modified to 'grade 4 neutropenia lasting for 8 days or longer accompanied by grade 4 leukopenia for at least 1 day during the period'. According to this amendment, none of the above-mentioned four patients met the criterion. (2) A patient whose neutrophils were not counted was determined to be ineligible. (3) An additional four patients would be enrolled to dose level 1 to determine the safety of the dose level. If DLT was observed in none or one of nine patients, the subsequent patients would be enrolled at dose level 2. If DLT was observed in two of nine patients, an additional three patients would be enrolled at dose level 1. If DLT was observed in three or four of nine patients, the study would be discontinued.

Response Evaluation

A secondary objective of the study was to evaluate the efficacy of the TAP regimen. The World Health Organization (WHO) criteria (15) were employed in this study. Complete response (CR) was defined as the disappearance of all gross evidence of disease for at least 4 weeks. Partial response (PR) was defined as a $\geq 50\%$ reduction in the sum of the products of the two largest perpendicular dimensions of all two-dimensionally measurable lesions and no evidence of new lesions for at least 4 weeks. No change (NC) was defined as a $<25\%$ increase or a $<50\%$ reduction in the sum of the aforementioned products and no evidence of new lesions for at least 4 weeks. Progressive disease (PD) was defined as a $\geq 25\%$ increase in the sum of the above-mentioned products or the appearance of any new lesions. Not evaluable (NE) was defined when insufficient data for response evaluation are available.

Before enrolling the patients into the study, the original protocol was approved by the Institutional Review Board (IRB) in each participating institute. The new protocol including the above-mentioned amendment was also approved by IRB in all participating institutes before restarting the study.

RESULTS

Patients' Characteristics

Between December 1998 and December 2000, 28 patients with advanced ovarian cancer were enrolled in this study. One patient was excluded from the study because sufficient laboratory data were not available for analysis. The median age of the 27 eligible patients was 56 years (range, 24–71 years) and 27 patients received 3–6 courses of chemotherapy (mean, 5.4 courses). Additional patients' characteristics are summarized in Table 1.

Dose Escalation and Dose-limiting Toxicity

Excluding one ineligible patient, whose neutrophils were not counted during the first course of chemotherapy, nine patients were enrolled into dose level 1. Among these nine patients, only one developed DLT, grade 4 diarrhea, so the dose escalation was allowed. The following six patients were enrolled into dose level 2. These six patients developed no DLT and further dose escalation was performed. The next six patients enrolled into dose level 3 did not develop DLT and the dose was escalated to level 4. Six subsequent patients were enrolled into dose level 4. Two patients developed DLT; one patient developed febrile neutropenia matching criterion (b) and grade 4 diarrhea and another patient developed prolonged grade 4 neutropenia matching criterion (a). The MTD defined in the protocol had not been reached even at dose level 4. Therefore,

Table 1. Patients' characteristics

Characteristic	No. of patients	%
Registered patients	28	–
Eligible patients	27	–
Stage		
III	24	88.9
IV	3	11.1
Histology		
Serous	23	85.2
Endometrioid	2	7.4
Clear cell	1	3.7
Undifferentiated	1	3.7
Residual disease		
0	4	14.8
0–1 cm	6	22.2
1–2 cm	4	14.8
>2 cm	13	48.1

it was decided to determine RD taking into account the toxicities of all cycles, the necessity of G-CSF support, the actual dose delivery and efficacy.

Hematological Toxicity

The hematological toxicity results are summarized in Table 2. The major toxicities observed were neutropenia and leukopenia. Grade 4 neutropenia was observed frequently even during the first course of chemotherapy [85% (23/27)] and almost all patients developed grade 4 neutropenia during all courses of chemotherapy [96% (26/27)]. The dose level was not correlated with the frequency of neutropenia (100% in level 1 and 83% in level 4 during the first course of chemotherapy). Grade 4 leukopenia was observed in 44% (12/27) of patients during the first course and in 52% (14/27) of patients during all courses of chemotherapy. The toxicity did not seem to increase from the second to sixth courses of chemotherapy. However, the frequency of grade 4 leukopenia was correlated with the dose level during the first course [22% (2/9) in level 1 to 83% (5/6) in level 4] and all courses of chemotherapy [22% (2/9) in level 1 to 83% (5/6) in level 4]. Among these grade 4 hematological toxicities observed during the first course of chemotherapy, toxicity developed by one patient in level 4 matched the dose-limiting toxicity criterion (a). As for other hematological toxicity, grade 3 anemia was rarely observed during the first course of chemotherapy [11% (3/27)]; however, nearly half of patients developed grade 3 anemia during all courses of chemotherapy [44% (12/27)]. Grade 4 thrombocytopenia was never observed during the first course of chemotherapy and only one patient developed grade 4 thrombocytopenia during all courses of chemotherapy [4% (1/27)].

Table 2. Hematological toxicity

Toxicity	No.(%) of grade 3/grade 4 toxicity			
	Level 1 (n = 9)	Level 2 (n = 6)	Level 3 (n = 6)	Level 4 (n = 6)
(A) During first course of chemotherapy				
Leukopenia	6 (67)/2 (22)	4 (67)/2 (33)	1 (17)/3 (50)	1 (17)/5 (83)
Neutropenia	0 (0)/9 (100)	1 (17)/4 (67)	0 (0)/5 (83)	1 (17)/5 (83)
Anemia	1 (11)/NA	0 (0)/NA	1 (17)/NA	1 (17)/NA
Thrombocytopenia	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
(B) During all courses of chemotherapy				
Leukopenia	6 (67)/2 (22)	3 (50)/3 (50)	1 (17)/4 (67)	1 (17)/5 (83)
Neutropenia	0 (0)/9 (100)	1 (17)/5 (83)	0 (0)/6 (100)	0 (0)/6 (100)
Anemia	2 (22)/NA	2 (33)/NA	6 (100)/NA	2 (33)/NA
Thrombocytopenia	0 (0)/0 (0)	1 (17)/0 (0)	2 (33)/0 (0)	1 (17)/1 (17)

Table 3. Non-hematological toxicity

Toxicity	No.(%) of grade 2/grade 3 toxicity			
	Level 1 (n = 9)	Level 2 (n = 6)	Level 3 (n = 6)	Level 4 (n = 6)
(A) During first course of chemotherapy				
Nausea and vomiting	2 (22)/1 (11)	2 (33)/1 (17)	3 (50)/0 (0)	2 (33)/1 (17)
Diarrhea	1 (11)/1 (11)	2 (33)/0 (0)	0 (0)/0 (0)	1 (17)/1 (17)
Alopecia	0 (0)/NA	0 (0)/NA	1 (17)/NA	2 (33)/NA
Neuropathy-sensory	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Hypersensitivity	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Renal toxicity	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Febrile neutropenia	NA/1 (11)	NA/0 (0)	NA/2 (33)	NA/2 (33)
(B) During all courses of chemotherapy				
Nausea and vomiting	5 (55)/1 (11)	2 (33)/1 (17)	4 (67)/0 (0)	4 (67)/1 (17)
Diarrhea	1 (11)/1 (11)	2 (33)/0 (0)	0 (0)/0 (0)	0 (0)/2 (33)
Alopecia	8 (88)/NA	5 (83)/NA	5 (83)/NA	5 (83)/NA
Neuropathy-sensory	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	1 (17)/0 (0)
Hypersensitivity	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Renal toxicity	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Febrile neutropenia	NA/2 (22)	NA/0 (0)	NA/2 (33)	NA/2 (33)

Non-hematological Toxicity

The results of non-hematological toxicity are listed in Table 3. Generally, non-hematological toxicity was mild or moderate. The observed grade 3 toxicities during the first course or all courses of chemotherapy were nausea and vomiting in 11% (3/27) or 11% (3/27), diarrhea in 7% (2/27) or 11% (3/27) and febrile neutropenia in 19% (5/27) or 22% (6/27), respectively. The frequency of above grade 3 toxicities did not increase during the second to sixth courses of chemotherapy and was not correlated with the dose levels. Among these grade 3 toxicities observed during the first course of chemotherapy,