Impact of Combination Chemotherapy with Itraconazole on Survival of Patients with Refractory Ovarian Cancer

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Abstract. *Background: After progression during chemotherapy, persistent ovarian cancer rarely responds to cytotoxic agents. We evaluated the use of adjunctive itraconazole for treating refractory ovarian cancer. Patients and Methods: Medical records of patients with ovarian cancer were retrospectively reviewed to select those with a history of platinum and taxane administration, clinical progression within six months of the last platinum administration, continuation of chemotherapy after the first progression during chemotherapy. Results: Among 55 patients, itraconazole in combination with chemotherapy was administered to 19 patients. The median progression-free survival (PFS) was 103 days and 53 days for chemotherapy with and without itraconazole, respectively (p=0.014). The corresponding median overall survival was 642 days and 139 days, respectively (p=0.006). The hazard ratio for PFS was 0.24 (p=0.002) and for overall survival was 0.27 (p=0.006) for therapy with itraconazole. Conclusion: Adjunctive itraconazole is promising for patients with refractory ovarian cancer.*

Ovarian cancer is an important cause of cancer-related death among women. According to the 2012 global cancer statistics, over 238,000 women were estimated to have had a diagnosis of epithelial ovarian carcinoma (EOC) (1). In most cases, patients present with advanced EOC and initially respond to platinum-based chemotherapy, typically consisting of carboplatin and paclitaxel. However, the majority of women experience relapse and subsequently do not respond to chemotherapy. In our previous report, the efficacy of continuing chemotherapy was assessed among patients who had received platinum and taxane chemotherapy, showed clinical progression within six months of their last dose of platinum, and progression during subsequent chemotherapy (R1). The response rate (RR) to conventional cytotoxic chemotherapy was 7.1%, and overall survival (OS) was only 168 days (2). Therefore, patients who had progressive disease during chemotherapy, or refractory disease, were considered poor responders to subsequent chemotherapy.

Acquired resistance to anticancer drugs observed in cases of ovarian cancer is not fully-understood. However, taxanes have been hypothesized to be transported by P-glycoprotein (P-gp, also known as multidrug resistance-1 or ATP-binding cassette sub-family B member ABCB-1), and P-gp expression is a marker for chemotherapy resistance and prognosis in ovarian cancer (3-5). In the late 20th century, itraconazole, a common anti-fungal agent, was shown, to reverse the P-gp-mediated resistance associated with paclitaxel, docetaxel, vinblastine, daunorubicin, and doxorubicin in a concentration-dependent manner *in vitro*, (6-8). In 2007, its potential for inhibiting angiogenesis was reported by a group at Johns Hopkins University School of Medicine (Baltimore, MD) (9). They identified itraconazole as a potential anticancer drug among the more than 3,000 US Food and Drug Administration-approved drugs tested. Survival benefit from the addition of itraconazole to chemotherapy was recently reported in a phase II randomized clinical trial of non-small cell lung cancer (NSCLC) and in our retrospective study of recurrent or persistent ovarian clear cell carcinoma, potentially chemotherapy-resistant histology (10,11).

To assess the efficacy of a combination of itraconazole and chemotherapy in patients with refractory ovarian cancer, we retrospectively compared outcomes of chemotherapy with and without itraconazole.

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Key Words: Itraconazole, chemotherapy, recurrent ovarian cancer, refractory disease.

Patients and Methods

The medical records of patients who had histologically-confirmed diagnoses of ovarian cancer and received treatment at our Hospitals between January 2004 and June 2013 were retrospectively reviewed. Patients were included if they had received platinum and taxane chemotherapy, showed clinical (symptomatic or radiological) progression within six months of their last dose of platinum, and continued chemotherapy after the disease first became refractory (R1). Those who progressed during the first-line treatment with platinum and taxane or during platinum-based chemotherapy at recurrence and who continued chemotherapy were included. The decision concerning whether to continue chemotherapy after R1 or to add itraconazole was based on a consensus among the attending physicians, the patient, and the patient's family, without any fixed criteria. Since targeted agents, including bevacizumab, were not approved for the treatment of ovarian cancer by the Ministry of Health, Labour, and Welfare of Japan at the time, none of these patients received targeted therapy, and none were enrolled in any clinical trial involving targeted therapy. This retrospective study was approved by our Institutional Review Boards (No. 1519).

Clinical and pathological features documented at the initiation of chemotherapy following R1 were reviewed. When the same regimen was administered, the number of regimens was recorded as 1. The platinum-free interval was calculated from the last date of platinum administration to the first date of chemotherapy after R1. Platinum-refractory disease was defined as clinical progression during prior platinum-based chemotherapy during either the first or any subsequent regimen.

The efficacy of subsequent chemotherapy after R1 was evaluated according to the Gynecologic Cancer InterGroup (GCIG) criteria, published in 2011 (12). Briefly, in patients with measurable disease, the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was applied (13); patients without measurable disease were evaluated by serum cancer antigen (CA)-125 levels. Because in routine clinical practice, computed tomographic (CT) slices were 5-10-mm thick, measurable lesions were defined as those ≥20 mm in diameter. The response rates were compared, using a chi-square test, between patients grouped based on whether they received adjunctive itraconazole after the R1. Progression-free survival (PFS) was defined as the time from the first day of chemotherapy after R1 to the date of objectively determined recurrence or progressive disease, health status deterioration attributable to disease, or death. OS was defined as the time from the first day of chemotherapy after R1 to death by any cause. Survival curves were estimated using the Kaplan–Meier method and compared between the groups treated with and without itraconazole using the log-rank test. A multivariate analysis was performed using the Cox proportional hazards regression model for PFS and OS after exposure to itraconazole, in combination with chemotherapy, after R1, adjusting for age, race, Eastern Cooperative Oncology Group (ECOG) performance status (PS), histology of the carcinoma, number of prior regimens, and platinum sensitivity status. All statistical analyses were conducted using XLSTAT 2012 (Addinsoft, Paris, France).

Results

Patients' characteristics. Between January 2004 and June 2013, 55 women were eligible for inclusion in the final analyses. Eighteen patients (33%) were referred from other hospitals after R1; 9 (16%) were older than 70 years of age. Chemotherapy after R1 was conducted in patients with an ECOG PS of 0-3; 12 patients (22%) had an ECOG PS of 3. Clear cell carcinoma represented 18% of all histological types. Eighteen patients (33%) received more than two prior treatment regimens, and 34 (62%) had experienced progression during a prior platinum-based treatment. After R1, 19 patients (35%) received itraconazole in combination with chemotherapy, and among those, 2 had prior chemotherapy with itraconazole. The overall patient characteristics are summarized in Table I. The regimens administered in combination with itraconazole after R1 were docetaxel-based chemotherapy in 15 (79%) patients, and chemotherapy combined with itraconazole was administered biweekly in 18 (95%) patients. An oral itraconazole solution was administered at a daily dose of 400-600 mg for 4-5 days (day −2 to day 2 or 3). The regimens without itraconazole included monotherapy in 23 (64%) patients, of whom 5 received pegylated liposomal doxorubicin, 5 gemcitabine, 4 docetaxel, 4 irinotecan, and 3 received paclitaxel.

Table I. *Patients' demographics (n=55).*

Age, years	Median (range), days	59 (38-83)
Race	Asian	54 (98%)
	Caucasian	1 (2%)
ECOG performance status	0	15 (27%)
	1	15 (27%)
	2	13 (24%)
	3	12 (22%)
Histology	Serous	33 (60%)
	Clear	10 (18%)
	Endometrioid	4 (7%)
	Other	8 (15%)
No. of prior regimens	1	18 (33%)
	2	19 (35%)
	3	7 (13%)
	≥4	11 (19%)
Platinum-free interval	Median (range), days	48 (12-891)
Platinum-refractory		34 (62%)
Prior treatment	Radiation	7 (13%)
	ITCZ	9 (16%)

ECOG, Eastern Cooperative Oncology Group; ITCZ, itraconazole.

Efficacy. One complete response and nine partial responses were observed among the eligible patients, yielding a chemotherapy RR of 18% [95% confidence interval (CI)=8-28%) after R1. Six patients (32%) responded to chemotherapy with itraconazole, whereas 4 (11%) responded to regimens without itraconazole (p=0.06). Among the eligible patients, the median PFS and OS periods were 77 days (95% CI=53-103 days) and 183 days (95% CI=134-250 days), respectively. The median PFS for patients with and

Table II. *Factors influencing progression-free survival (PFS) and overall survival (OS) after the disease first became refractory (n=55).*

		PFS			OS		
	Variable	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI
Age, years	>60 vs. ≤60	0.41	1.4	0.65-2.9	0.69	0.88	0.45-1.7
ECOG PS	2 vs. 0-1	0.50	0.75	0.33-1.7	0.18	0.55	0.23-1.3
	3 vs. 0-1	0.10	2.0	0.87-4.6	0.19	1.7	0.76-3.9
Histology	S/E vs. other	0.96	0.98	0.47-2.1	0.61	0.82	0.38-1.8
No. of prior regimens	≥3 vs. 2	0.07	0.47	0.21-1.1	0.79	0.90	0.42-1.9
	1 vs. 2	0.46	0.71	0.29-1.8	0.66	1.3	0.50-3.0
Platinum refractory	No vs. yes	0.40	0.73	0.35-1.5	0.66	1.2	0.56-2.5
Chemo w/wo ITCZ	With vs. without	0.002*	0.24	0.10-0.60	0.006*	0.27	0.11-0.68

ECOG, Eastern Cooperative Oncology Group; PS, performance status; N, number; Chemo, chemotherapy; w/wo, with or without; ITCZ, itraconazole; S/E, serous and endometrioid; HR, hazard ratio; 95% CI, 95% confidence interval. *$p<0.05$ for multivariate analysis using the Cox proportional hazards model.

without itraconazole was 103 days (95% CI>84 days) and 53 days (95% CI=38-88 days), respectively ($p=0.014$) (Figure 1), whereas the corresponding median OS was 642 days (95% CI=238-1166 days) and 139 days (95% CI=89-183 days), respectively ($p=0.006$) (Figure 2). Multivariate analysis revealed that administration of itraconazole with chemotherapy impacted on both PFS and OS. The hazard ratio for PFS was 0.24 (95% CI=0.10-0.60; $p=0.002$) and for OS was 0.27 (95% CI=0.11-0.68; $p=0.006$) with therapy with itraconazole (Table II).

Discussion

The real benefit of chemotherapy for platinum-resistant or refractory disease in patients with ovarian cancer is that it has been proposed to control symptoms, maintain quality of life (14), and instill positivity in patients by allowing them to continue chemotherapy or present them with an alternative treatment (15). For platinum-resistant disease, only one randomized clinical trial has shown a survival benefit associated with conventional chemotherapy (16). In that study, all patients had an ECOG PS of 0 or 1, and the number of prior regimens was fewer than three. Additionally, only 14% of patients had a history of refractory disease. Until recently, randomized clinical trials had not demonstrated a survival benefit for any cytotoxic agent or combination chemotherapy in refractory disease.

To improve the efficacy of chemotherapy, intrinsic and acquired resistance to anticancer drugs need to be addressed. Simultaneous resistance also occurs for agents that have not been used in prior chemotherapy and differ in chemical structure or mode of action. One of the most extensively studied mechanisms of resistance involves the P-gp-mediated efflux system (17). In a phase II clinical trial, a second-generation P-gp modulator, VX-710 (biricodar), was administered to patients with ovarian cancer (18). Among the 45 evaluable patients who experienced disease progression during or within four months of paclitaxel administration, three responded to rechallenge with paclitaxel and VX-710; disease in two out of the three individuals had progressed during their prior paclitaxel therapy. Another second-generation P-gp modulator, valspodar (PSC 833), was reported in a phase III study of front-line chemotherapy for ovarian cancer. Compared with the standard chemotherapy of paclitaxel and carboplatin, the paclitaxel dose was reduced from 175 mg/m^2 to 80 mg/m^2 in combination with valspodar. The addition of valspodar to standard chemotherapy regimens did not improve the duration of PFS or OS, but did increase the number of adverse events (19). Because drug–drug interactions involving cytochrome P450, family 3, subfamily A (CYP3A) inhibition required reduction of cytotoxic drug dose, the third-generation P-gp inhibitor, tariquidar (XR9576), with increased specificity and potency, and fewer pharmacokinetic interactions was tested in combination therapy. The docetaxel dose of 75 mg/m^2 every three weeks could be safely administered in the combination (20). Among 18 patients with ovarian cancer, one had a partial response to XR9576 and docetaxel, but her prior treatment was not described. However, two phase III studies in advanced NSCLC, combining tariquidar with carboplatin/paclitaxel or with vinorelbine, closed early due to toxicity. The concept of reversing drug resistance has been demonstrated successfully in preclinical studies, but has failed in clinical trials or is not expected to be included in further clinical investigations. The current exploratory analysis showed the impact of combining chemotherapy with itraconazole on OS.

Based on a pre-clinical study of angiogenesis inhibition, experts at the Johns Hopkins School of Medicine conducted a randomized phase II trial of itraconazole in NSCLC (10).

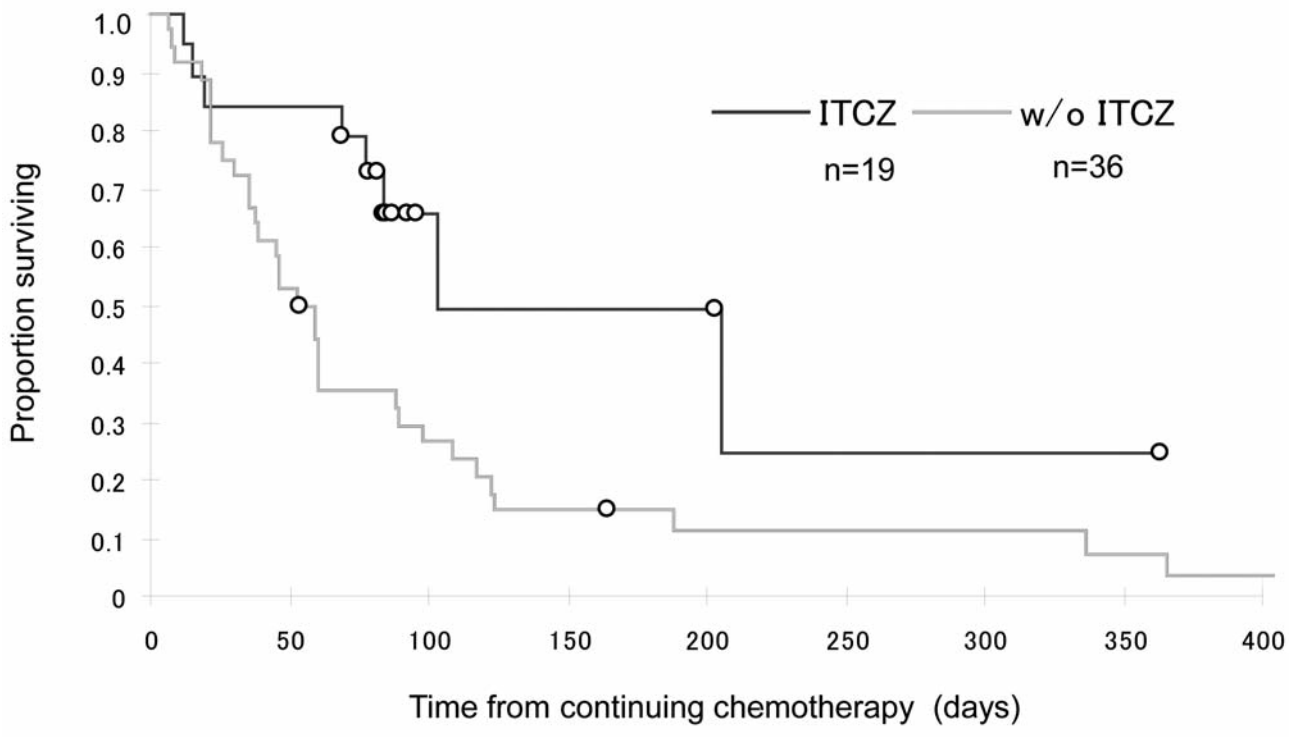

Figure 1. *Progression-free survival (PFS) after continuing chemotherapy with or without (w/o) itraconazole (ITCZ) after the disease first became refractory. Median PFS was 103 days (95% confidence interval >84 days) and 53 days (95% confidence interval=38-88 days) for chemotherapy with and without ITCZ, respectively (p=0.014).*

Concomitant pemetrexed and itraconazole therapy did not yield an improved PFS compared to therapy without itraconazole in the 23 enrolled patients; however, the OS was significantly longer among patients receiving itraconazole (p=0.012). The authors suggested that the reason for the OS advantage associated with itraconazole administration was, therefore, due to the anti-angiogenesis effects of itraconazole. They also noted the comparison between itraconazole and bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor. In addition, the ECOG 4599 trial demonstrated a statistically significant (2-month) improvement in OS, with more severe toxicities (the incidence of treatment-related deaths was 3.5%) when bevacizumab was administered (21). However, a confirmatory trial (AVAiL) did not demonstrate an OS benefit (22). For EOC-targeted therapy, bevacizumab is also the most extensively studied agent. Two randomized trials, GOG218 and ICON7, demonstrated prolonged PFS when bevacizumab was administered as the first-line induction and maintenance chemotherapy, but an OS benefit was not observed (23, 24). The GOG 218 study demonstrated a 3.8-month improvement in PFS with an additional 51 weeks of treatment, a 10% risk of grade 3-4 hypertension, and a 2.3% risk of grade 3 or worse gastrointestinal perforation, hemorrhage, or fistula formation (25). However, Cohen *et al*. reported that the addition of bevacizumab was not cost-effective (26). Furthermore, in the randomized trials for recurrent EOC, bevacizumab did not prolong OS (27, 28). Considering the results of clinical trials involving patients with EOC and NSCLC, the survival advantage of itraconazole-treated patients in our study and in the Johns Hopkins trial is extraordinary and cannot be fully explained by the anti-angiogenesis effects of itraconazole when administered in combination with chemotherapy. In the present study, patients who suffered recurrence after chemotherapy combined with itraconazole were treated with other cytotoxic regimens and rechallenged with itraconazole. In colorectal cancer, the continuous use of bevacizumab, beyond disease progression, has been shown to prolong OS (29, 30). In ovarian cancer, a retrospective study showed that re-treatment with bevacizumab prolonged PFS but not OS (31). The favorable OS in the current study might be associated with the continued use of itraconazole, which produced fewer toxicities and cost less than bevacizumab.

Recent trends in the development of anticancer agents have focused on cancer stem cells (CSCs) to prolong OS or even offer a cure. CSCs are drug-resistant (32), with one of the chemoresistance mechanisms involving P-gp-mediated efflux

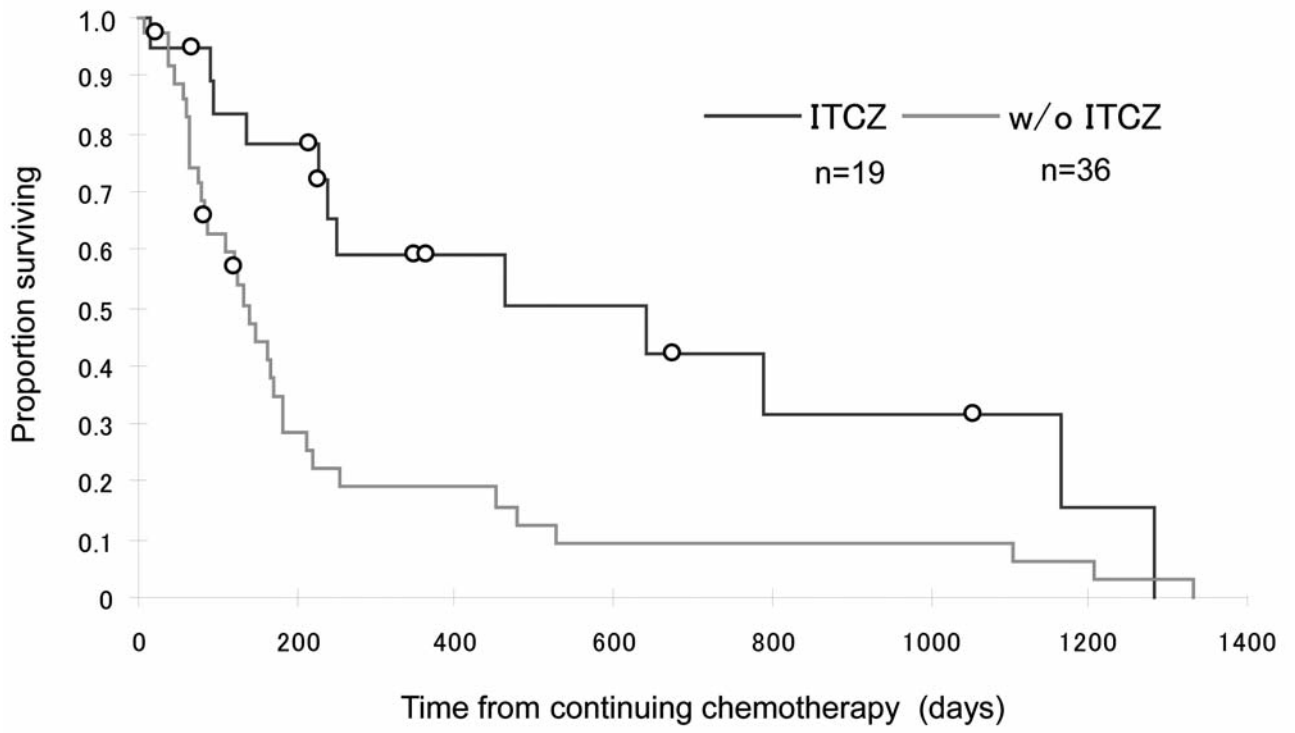

Figure 2. *Overall survival (OS) after continuing chemotherapy with or without (w/o) itraconazole (ITCZ) after the disease first becoming refractory. Median OS was 642 days (95% confidence interval=238-1166 days) and 139 days (95% confidence interval=89-183 days) for chemotherapy with and without ITCZ, respectively (p=0.006).*

of cytotoxic agents (33). Self-renewal, multi-lineage differentiation, and metastatic development by CSCs are processes associated with the hedgehog signaling pathway (34). CSCs and the hedgehog signaling pathway have also been reported to play important roles in the development and progression of EOC (35–37). As a result, hedgehog inhibitors have been investigated in clinical trials. A phase II randomized trial of saridegib (IPI-926), a synthetic derivative of cyclopamine (11-deoxyjervine), for the treatment of metastatic pancreatic cancer was terminated after an interim analysis demonstrated a more favorable OS rate in the placebo-plus-gemcitabine arm (38). A phase II randomized trial of vismodegib, approved for treatment of advanced basal cell carcinoma by the United States Food and Drug Administration in 2012, demonstrated that its addition to gemcitabine did not improve response, PFS, or OS in patients with metastatic pancreatic cancer (39). Itraconazole also inhibits the hedgehog signaling pathway, but does so by a mechanism distinct from that of either saridegib or vismodegib (40).

Various cytotoxic regimens were administered in combination with itraconazole in this retrospective study. Until recently, RR has been considered to possibly increase if combination therapies were administered; however, PFS or OS did not substantially change. Therefore, further investigation into the cytotoxic agents administered in combination with itraconazole should be conducted to betters determine related toxicities, and interference with CYP3A and the blood–brain barrier by itraconazole (41). In patients with leukemia, itraconazole has been used prophylactically to prevent fungal infections (42, 43). Over 300 patients with recurrent or persistent gynecological or non-gynecological cancer have been treated in our hospital with chemotherapy in combination with itraconazole, without any reported deaths or serious adverse events. Thus, current limited experience suggests that itraconazole combination therapy is a comparatively safe treatment option for refractory disease.

Our study has some limitations. Data had to be pooled retrospectively from different Hospitals owing to the small number of eligible patients, as most patients discontinued chemotherapy before or at R1 (2). Additionally, other prognostic or predictive factors might have been missed in the multivariate analysis. Nevertheless, the results of this study are encouraging for patients who wish to continue chemotherapy after R1, taking advantage of the efficacy and limited toxicity of itraconazole. Furthermore, itraconazole is not an expensive drug, and thus, its use could be affordable for patients in less-developed countries and might reduce treatment costs in developed countries.

Conflicts of Interest

The Authors have no financial conflicts of interest to disclose.

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Received January 17, 2014
Revised February 22, 2014
Accepted February 24, 2014