ORIGINAL ARTICLE

UDC: 577.2:616.33-006
https://doi.org/10.2298/VSP180205048E

Significance of KIT and PDGFRA mutations in gastric gastrointestinal stromal tumor imatinib-naive surgically treated patients

Značaj mutacija KIT i PDGFRA kod bolesnika operisanih zbog gastrointestinalnog stromalnog tumora želuca bez primene imatiniba

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Abstract

Background/Aim. KIT (KIT proto-oncogene receptor tyrosine kinase) and PDGFRA (platelet-derived growth factor receptor alpha) gene mutations represent major molecular forces inside the gastrointestinal stromal tumors (GIST). Aim of this study was to evaluate these mutations in the patients who underwent surgical resection of gastric GIST, but without imatinib mesylate treatment. **Methods.** Retrospective clinical study included patients who were operated on due to gastric GIST from November 2000 till November 2016. A molecular analysis of paraffin embedded tumor tissue was performed, and the patients with the presence of KIT and PDGFRA mutations were further evaluated, with regard to the pathological tumor stage, disease recurrence and overall survival. **Results.** Out of 45 patients in total, 43 patients had KIT and PDGFRA mutations, and 2 patients were classified as the wild type GIST. After curative resection, 11 patients were classified as a low risk GIST, 8 as an intermediate risk and 26 as a high risk GIST. The KIT mutations were present in 37 patients, most commonly as deletion in exon 11. The PDGFRA mutations were present in 6 patients. The presence of KIT mutation had a strong statistical correlation with the mitotic index ($p = 0.021$). After the ten-year follow-up, all patients with the PDGFRA mutations were alive, while those with the KIT mutations had a survival rate of 71% ($p = 0.31$). **Conclusion.** The presence of KIT exon 11 deletion in the patients with primarily resected gastric GIST is associated with the higher mitotic index and worse overall survival than those present with the PDGFRA mutations. This results suggest prognostic significance towards more aggressive behaviors.

Key words:
gastrointestinal stromal tumors; genes; mutation; digestive system surgical procedures; neoplasm metastasis; prognosis; survival.

Apstrakt

Uvod/Cilj. KIT (KIT *proto-oncogene receptor tyrosine kinase*) i PDGFRA (*Platelet-derived growth factor receptor alpha*) genske mutacije predstavljaju osnovne molekularne promene u grupi gastrointestinalnih stromalnih tumora (GIST). Cilj ove studije bio je da se analiziraju KIT i PDGFRA mutacije u grupi bolesnika koji su operisani zbog primarnog GIST-a želuca, ali bez terapije imatinib mesilatom. **Metode.** Načinjena je retrospektivna klinička studija koja je uključila bolesnike operisane zbog GIST-a želuca u periodu od novembra 2000. do novembra 2016. godine. Načinjena je molekularna analiza na parafinskim kalupima tumorskog tkiva, a kod bolesnika kod kojih su identifikovane KIT i PDGFRA mutacije sprovedena je dalja analiza, sa posebnim osvrtom na patološke karakteristike tumora, recidiv oboljenja i ukupno preživljavanje, te procena uticaja analiziranih genskih mutacija na navedene promene. **Rezultati.** Od ukupno 45 bolesnika, 43 bolesnika imala su prisutne mutacije na KIT i PDGFRA genima, dok su dva bolesnika klasifikovani kao "*wild type*" GIST. Po učinjenoj kurativnoj resekciji, 11 bolesnika je klasifikovano u grupu GIST-a niskog stepena, 8 u grupu srednjeg, a 26 bolesnika u grupu visokog rizika od metastaziranja. KIT mutacije su bile prisutne kod 37 bolesnika, najčešće u formi deleciji na egzonu 11. PDGFRA mutacije bile su prisutne kod 6 bolesnika. Prisustvo KIT mutacija imalo je visoku statističku korelaciju sa mitotiskim indeksom ($p = 0,021$). Nakon desetogodišnjeg praćenja, svi bolesnici iz grupe sa PDGFRA mutacijama su bili živi, dok je stepen preživljavanja bolesnika sa KIT mutacijama iznosio 71% ($p = 0,31$). **Zaključak.** Prisustvo KIT egzon 11 delecija kod bolesnika kod kojih je sprovedena primarna hirurška intervencija zbog GIST-a želuca povezana je sa visokim mi-

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totskim indeksom i lošijem ukupnom preživljavanju, ali bez statistički značajne razlike u odnosu na bolesnike kod kojih je bila prisutna PDGFRA mutacija. Ovi rezultati ukazuju na prognostički značaj u pravcu agresivnog ponašanja tumora.

Ključne reči:
gastrointestinalni stromalni tumori; geni; mutacija; hirurgija digestivnog sistema, procedure; neoplazme, metastaze; prognoza; preživljavanje.

Introduction

Gastrointestinal stromal tumor (GIST) represents a most common mesenchymal neoplasm of the digestive system [1]. These tumors can be located in every part of alimentary tract, but most frequently GISTs are encountered in stomach [2].

Gastrointestinal bleeding is leading symptom, followed with dyspepsia, abdominal pain and discomfort, but its presentation can range from palpable masses in the abdomen to completely asymptomatic ones [3]. Unlike the carcinomas, GISTs lack dominant infiltrative type of growth, and rarely can involve the lymph nodes. However, once these tumors have reached the malignant potential, very aggressive hematogenous spread may occur, predominantly affecting the liver. This malignant potential in GISTs is outlined by three major factors, tumor site (location), size, and mitotic rate, and the risk systems based on these factors: were proven and implemented in rutine clinical practice [4]. Genetic alterations in GIST are relatively well-known, mostly through the assessments of tyrosine kinases inhibitor KIT and the platelet-derived growth factor receptor alpha (PDGFRA) gene mutations. Both genes play crucial role in GIST pathogenesis, as their activation has significant influence on the cell proliferation, apoptosis and other important cell functions [5].

Molecular changes in KIT and PDGFRA genes represent lead driving power in pathogenesis of gastrointestinal stromal tumors. These genes are the members of tyrosine kinase receptors, type III [6, 7]. With knowledge that kinase receptors play significant role in the treatment of GIST patients, proper understanding the mutations in KIT and PDGFRA may have a beneficial role in further understanding of tumor biology and subsequently may help in making proper decisions in each individual GIST patient. Various types of PDGFRA and KIT mutations in GISTs are frequently described in the relevant literature so far. Concerning the KIT gene, the mutation in exon 11 is most commonly described, followed with the mutations in exon 9, seldom in exons 13 and 17 [8]. Deletion mutation in exon 11 (codons 557 and 558) was linked to more aggressive clinical course of the disease [9]. On the other hand, the PDGFRA mutations, most frequently encountered in exons 12, 16 and 18, are less frequent than the KIT mutations, but their presences is associated with favorable pathologic and clinical tumor behavior [10, 11].

Clinical studies on KIT and PDGFRA in gastric GIST so far have been able to prove the significance of these mutations on tumor behavior, mostly reflected in disease relapse, metastatic potential and overall survival, although the studies that brought up this issue tended to have conflicting findings [12]. This might be due to the fact that various mutations can be encountered, for example in KIT exon 11, differently affecting tumor's biology [13, 14].

The aim of this study was to evaluate the significance of KIT and PDGFRA mutations as prognostic factors in correlation to metastatic potential and overall survival in the patients who underwent primary surgical treatment of gastric GIST.

Methods

This is the retrospective clinical study conducted at the Department for Esophagogastric Surgery, First Surgical University Hospital, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade. The molecular analysis was performed in a genetic laboratory, at the Institute for Neurology, Clinical Center of Serbia, Faculty of Medicine, Belgrade. It included the patients who were submitted to primary curative surgical treatment of gastric GIST without prior imatinib mesylate treatment, from November 2000 till November 2016. The Hospital Board and the Ethics Committee approved the study.

A database was created by the assessment of medical records and it included the following: demographic and clinical data, location and tumor size, type of surgical intervention, pathological and immunohistochemical examination. The follow-up records were collected prospectively and assessed the data regarding the tumor recurrence, or metastasis onset. The preoperative diagnostics was performed in all cases and it consisted of barium swallow radiography, esophagogastroduodenoscopy, endoscopic ultrasonography, computed tomography (CT) scan of thorax and abdomen.

The pathological reports were retrospecitvelly reviewed with respect to the resection margins, tumor size (the largest diameter was taken into acount), cellularity, cell type and mitotic index per 50 HPF (*High Power Field*). The immunohistochemical report included immunophenotype determination (positivity for CD117, CD34, α-SMA, desmin, S-100). The risk assessment and postoperative stratification in three categories was performed based on the criteria recommended by the National Institutes of Health (NIH), depending on the tumor site, size and mitotic index respectively.

The follow-up protocol included the clinical examinations and CT scans. The patients with the high and intermediate risk GIST were examined every 4 months during the first 3 years, followed by every 6 months during the next 2 years and once a year thereafter. The patients with a low risk GIST were examined yearly during 5 years.

Molecular analysis

The molecular genetic analysis was performed in the KIT and PDGFA genes, derived from the formalin fixed paraffin-embedded tumor samples. After the identification of tumor tissue, the sample sized 1 × 1 cm was chosen for the DNA extraction. After the paraffin removal, DNA was extracted by using the phenol-chloroform method. Isolated DNA was subsequently used for the mutations analysis in selected exons KIT and PDGFRA genes with the direct sequencing method according to Sanger. The PCR amplifica-

tion of desired regions was performed with specific primers (Verity Thermal Cycler, Life Technology, USA). This was followed by the PCR purification, and sequencing by using the BigDye Terminator v 3.1 Cycle Sequencing kit (Life Technology, USA). The sample analysis was performed by the capillary electrophoresis method using the ABI 3500 Genetic Analyzer, and for the software data processing, the Sequencher program version 4.10.1. was applied.

The presence of mutation in KIT and PDGFRA was the main inclusion criteria. Out of overall patient sample (n = 100), 43 patients had mutations in KIT and PDGFRA and 2 patients were classified as the wild type and were the subject of further analysis. Remaining 55 patients, in whom the curative surgical treatment of gastric GIST was conducted, did not possessed a tissue sample of sufficient quality for the genetic analysis. Significantly, none of the patients received KIT, so all analyses were performed in imatinib mesylate-naive tumor sample.

Statistical analysis

The data are expresed as means with percentages and standard deviations. The statistical correlations between different pathological parameters were tested by using the χ^2 test and the Fischer's extact test. The survielance curve was created using the Kaplan-Meier method, and a statistical significance was tested with the log-rank test. The level of statistical significance was set at 0.05. All analyses were performed by using the statistical software SPSS version 15.0.

Results

Overall, the study included 45 patients, of whom 21 men, and 24 women, who met the inclusion criteria. The mean age of study population was 59.1 years (range from 23 to 84 years). Bleeding was the predominant symptom in the disease presentation in 22 patients, followed by the abdominal pain in 10 patients and the abdominal discomfort in 6 patients, while dysphagia was present in 2 patients and 1 patient had the abdominal palpable mass. There were 4 asymptomatic patients.

Primary curative surgical treatment was conducted in all patients. Table 1 presents the range of surgical interventions which were performed. There was no postoperative morbidity nor mortality in the study.

After the pathological examination, 26 patients were classified as high risk GIST, 8 and 11 as intermediate and low risk, respectively, while none of the patients fulfilled the criteria for very low risk. The detailed clinical, pathological and imunohistochemistery data are given in Table 2.

The mean length of follow-up was 61.77 months (ranging from 9 to 142 months).

Table 2

Clinical and pathological characteristics of gastrointestinal stromal tumor (GIST) patients

Parameters	Values
Sex, n (%)	
male	21 (49)
female	24 (51)
Age (years), mean (range)	59 (23–84)
Symptoms, n (%)	
melena	20 (44)
haematemesis	2 (4)
abdominal pain	10 (22)
abdominal discomfort	6 (13)
dysphagia	2 (4)
palpabil mass	1 (2)
asymptomatic	4 (8)
Tumor longest diameter (mm), Mean (range)	77.84 (22–210)
Tumor dimension grups, n (%)	
≤ 2 cm	0
> 2 ≤ 5 cm	13 (29)
> 5 ≤ 10 cm	23 (51)
> 10 cm	9 (20)
Mitosis, n (%)	
≤ 5/50 HPF	24 (53)
> 5/50 HPF	21 (47)
Necrosis, n (%)	
absent	31 (69)
focal	12 (27)
spread	2 (4)
Anaplasia, n (%)	
low	43 (96)
high	2 (4)
Cellulary type, n (%)	
spindele	36 (80)
epithelioid	3 (7)
mixed	6 (13)
CD 117, n (%)	
-	6 (13)
+	39 (87)
CD 34, n (%)	
-	6 (13)
+	39 (87)
SMA, n (%)	
-	31 (69)
+	14 (31)
Resection margins, n (%)	
R0	45 (100)
R1	0
NIH risk, n (%)	
very low	0
low	11 (24)
intermediate	8 (18)
high	26 (58)

Table 1

Surgical management of the gastrointestinal stromal tumors and risk classification

Type of surgery	Low risk (n = 11)	Intermediate risk (n = 8)	High risk (n = 26)	Total (n = 45)
Wedge resection, n (%)	9 (20)	8 (18)	10 (22)	27 (60)
Subtotal gastrectomy, n (%)	1 (2)	0 (0)	4 (9)	5 (11)
Total gastrectomy, n (%)	1 (2)	0 (0)	10 (22)	11 (24)
Distal esophagectomy and total gastrectomy, n (%)	0 (0)	0 (0)	2 (5)	2 (5)

Table 3

Follow-up data of gastrointestinal stromal tumor (GIST) patients

Occurence of metastases	Total of number of patients (45) n (%)
Metastasis or local recurrence	
intraoperative metastasis	2 (4)
metastasis during follow-up	9 (20)
local recurrence during follow-up	3 (7)
no metastasis / recurrences	31 (69)
Mean time to metastasis/recurrence in months	24.83
Current status	
ANED	31 (69)
AWD	5 (11)
DOD	7 (16)
DUC	2 (4)

ANED – alive no evidence of disease; AWD – alive with disease; DOD – died of disease; DUC – died of unrelated causes.

Table 3 presents a proportion of patients with liver metastasis on admission, who were submitted to surgery due to bleeding from the primary tumor site, the patients who developed liver metastasis and a local recurrence during the follow-up period, and the patients who are disease free.

The median interval from the surgery to occurrence of metastasis, or a local recurrence was 24.83 months (2–92 months). Two patients, who had liver metastases diagnosed intraoperatively, were submitted to metastasectomy, R0 resection was reached, and the postoperative course went uneventfully.

Molecular analysis

The molecular analysis showed that the genetic mutations in KIT and PDGFRA were present in 43 patients, while 2 cases were classified as the wild type GIST. A simplified presentation of genetic mutations in KIT and PDGFRA is shown in Table 4.

Table 4

Distribution of KIT and PDGFRA mutations

Type of mutation	Total of number of patients (45) n (%)
KIT	37 (82)
Exon 9	
insertion	1 (2)
deletion	2 (4)
point mutation	2 (4)
Exon 11	
insertion	3 (7)
deletion	18 (45)
insertion-deletion	3 (7)
point mutation	8 (18)
PDGFRA	6 (13)
Exon 12	
deletion	1 (2)
Exon 16	
point mutation	1 (2)
Exon 18	
point mutation	4 (9)
Wild type KIT/PDGFRA	2 (5)

PDGFRA – platelet-derived growth factor receptor alpha.

The KIT mutations were present in 37 patients. Out of those, 18 patients had deletion on exon 11, 3 patients had insertion, 3 had the combination of insertion and deletion, while the point mutation was present in 8 of them. The exon 9 mutations were present in 5 patients, the deletion and point mutation in 2, and insertion in 1 patient. The PDGFRA mutations were present in 6 patients. Out of those, 4 patients had presence of point mutations on exon 18, while 1 had deletion on exon 12 and 1 the point mutation on exon 16.

The correlation between the pathological parameters and types of genetic mutation was shown in Table 5. A statistically significant correlation was found between the mitotic rate and KIT mutations ($p = 0.021$). There was no statistical correlation between other pathological parameters and analyzed genetic mutations.

The Kaplan-Meier curve, as well as 1, 5 and 10 years of survival rates with regard to the type of mutation are presented in Figure 1. Overall survival rate for the patients with the proven KIT gene mutation was 71% (91%, 78% and 71% during 1, 5 and 10 years, respectively). In the patients without these mutations overall survival rate was 85% (94%, 85% and 85% during 1, 5 and 10 years respectively). The patients with the proven PDGFRA mutations had the overall survival rate 100%. Both patients with the wild type mutations were also alive and disease free through the follow-up period. There were no statistically significant differences between the overall survival and the type of mutations ($p = 0.310$).

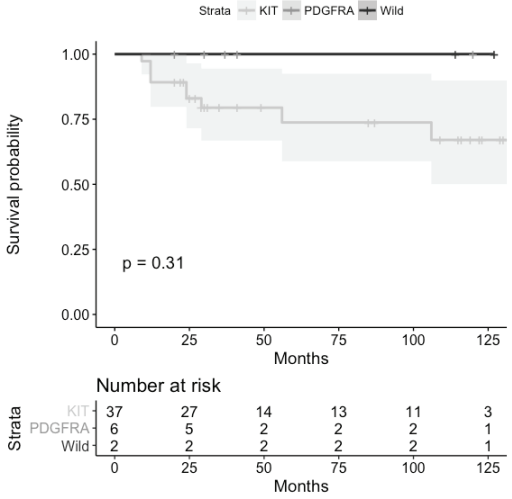

Fig. 1 – Kaplan –Meier curve showing overall survival rates with regard to different genetic mutation type. PDGFRA – platelet-derived growth factor alpha.

Table 5

Correlation between the pathological and molecular parameters

	KIT exon 9 mutations, n (%)			KIT exon 11 mutations, n (%)					PDGFRA mutations, n (%)			
	Ins	Del	PM	Ins	Del	Ins-del	PM	*pp*	Exon 12 Del	Exon 16 PM	Exon18 PM	*p*
Cell type												
spindle	1 (100.0)	0 (0.0)	2 (100.0)	3 (100.0)	15 (83.3)	2 (66.7)	7 (87.5)		1 (100.0)	0 (0.0)	3 (75.0)	
epitheloid	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (12.5)	0.550	0 (0.0)	0 (0.0)	1 (25.0)	0.400
mixed	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	2 (11.1)	1 (33.3)	0 (0.0)		0 (0.0)	1 (100.0)	0 (0.0)	
Mitotic count												
≤ 5/50 HPF	0 (0.0)	0 (0.0)	2(100.0)	2 (66.7)	6 (33.3)	1 (33.3)	7 (87.5)	0.021	1 (100.0)	1 (100.0)	2 (50.0)	1.000
> 5/50 HPF	1 (100.0)	2(100.0)	0 (0.0)	1 (33.3)	12 (66.7)	2 (66.7)	1 (12.5)		0 (0.0)	0 (0.0)	2 (50.0)	
Tumor necrosis												
absent	1 (100.0)	1 (50.0)	2 (100.0)	1 (33.3)	11 (61.1)	1 (33.3)	7 (87.5)		1 (100.0)	1 (100.0)	3 (75.0)	
focal	0 (0.0)	1 (50.0)	0 (0.0)	2 (66.7)	5 (27.8)	2 (66.7)	1 (12.5)	0.613	0 (0.0)	0 (0.0)	1 (25.0)	1.000
spread	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Anaplasia												
low	1 (100.0)	2 (100.0)	2 (100.0)	3 (100.0)	17 (94.4)	3 (100.0)	8 (100)	1.000	1 (100.0)	1 (100.0)	4 (100.0)	1.000
high	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
NIH score												
very low	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	4 (22.2)	0 (0.0)	4 (50.0)		0 (0.0)	1 (100.0)	1 (25.0)	
low	0 (0.0)	0 (0.0)	1 (50.0)	1 (33.3)	2 (11.1)	1 (33.3)	2 (25.0)	0.145	1 (100.0)	0 (0.0)	1 (25.0)	1.000
intermediate	0 (0.0)	1 (50.0)	1 (50.0)	1 (33.3)	1 (5.6)	1 (33.3)	1 (12.5)		0 (0.0)	0 (0.0)	0 (0.0)	
high	1 (100.0)	1 (50.0)	0 (0.0)	0 (0.0)	11 (61.1)	1 (33.3)	1 (12.5)		0 (0.0)	0 (0.0)	2 (50.0)	

***Ins – insertion; Del – deletion; PM – point mutation; NIH – National Institutes of Health.**
For other abbreviations see under Table 4.

Discussion

The results of this study implicated that the KIT gene mutations are the most common type of mutation in gastric GIST. Although the clinical relevance of these mutations in our patient population was not clearly shown, in the discussion bellow we will try to make a thorough analysis and draw out relevant conclusion.

In the overall patient sample KIT and PDGFRA mutations were present in 45% of patients, predominantly KIT mutations in exon 11, while PDGFRA mutations were observed in 6 patients. These frequencies are lower than those noted in the literature reports so far, where the occurrence of KIT mutations was reported to be around 80%, and PDGFRA approximately about 10%. This can be explained by the retrospective nature of the study and the possibility that some of tumor samples were not preserved sufficiently to contain DNA suitable for further analysis. Yet, the overall distribution of molecular changes in this study population, reflected in the KIT versus PDGFRA mutations ratio as well as frequencies of mutation types, is in accordance to the literature results [15].

The KIT mutation was the predominant type of mutation in our study and the leading type of mutation was deletion in exon 11. This is in concordance with the report of Joensuu et al. [16], who based their study on an analysis of 11 literature reports concerning the KIT and PDGFRA mutations in GIST. The authors confirmed that the KIT mutations in exon 11 were the most common type of mutation, and presented in 293 out of 301 analyzed patients. Deletion was most common type of mutation, presented in 43% of patients. Concerning the relation of this specific mutation and other pathological parameters of GIST, our study showed that the presence of this mutation had a strong statistical correlation with the higher mitotic index. However, there was no correlation with other pathological parameters. The results of published studies shows that KIT mutations in exon 11 can be linked with more aggressive tumor behavior [17, 18]. Capelli et al. [19] showed that the patients with gastric GIST who had the KIT mutations, were presented with worse pathological parameters, such as tumor necrosis, spindle cellularity, tumor size and mitotic index. Similar results were noted by Schaefer et al. [20].

The PDGFRA mutations were by far less present in our study than the KIT mutations, which is concordance with other literature reports being around 6%. The most common type of PDGFRA mutation noted in our study was the point mutation on exon 18. There was no statistical correlation between these molecular changes and the analyzed pathological parameters. Lasota and Miettinen [14] found that the majority of GIST patients with the presence of PDGFRA mutation had predominantly the epitheloid type of tumor, with the low mitotic index and benign clinical course.

In our study, the overall survival rate among the patients who had the KIT mutations during the 10-year follow-up was 71%, while in those GIST patients with the PDGFRA mutations there was no mortality in the follow-up period. Although there is a tendency towards better overall survival in the group of patients with the PGFRA mutations, a statistical significance was not reached probably due to a small sample size inside this group. Our study involved the patients who did not receive any prior imatinib mesylate therapy. Rossi et al. [21] published their results concerning imatinib-naive GIST patients with regard to a tumor mutational status and confirmed that the KIT mutations were the independent prognostic factors of poor overall survival. The authors also identified several groups according to the mutation status and they were those with an increased risk of tumor recurrence and metastasis. Those with the greatest malignant potential had mutations in KIT exon 9 and 11, and PDGFRA in exon 18 apart from D842V.

Limitations of this study include a relatively small sample of patients and the retrospective method.

Conclusion

A risk stratification for gastric GIST is well- established and based on clinically proven classifications based on the tumor site, size and mitotic rate. The recognition and assessment of KIT and PDGFRA mutations in these tumors may play a significant role as an additional factor in the risk stratification, disease prognosis, but may be important to identify the patients who are at the highest risk for disease recurrence.

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Received on February 5, 2018.
Revised on March 1, 201.
Accepted on March 11, 2018.
Online First March, 2018.