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Systemic steroid for severe skin rash induced by imatinib in patients with GIST: A phase II study

[1]울산대학교 의과대학 서울아산병원 내과, [2]울산대학교 의과대학 서울아산병원 종양내과, [3]울산대학교 의과대학 서울아산병원 피부과

*김어진[1], 류민희[2], 박숙련[2], 백모열[2], 이우진[3], 이미우[3], 강윤구[2]

Background/Aims: To achieve optimal clinical outcomes with imatinib in GIST patients, it is crucial to maintain standard dose of imatinib. Skin rash is a common and sometimes severe adverse event of imatinib treatment and may affect compliance of imatinib. Our previous retrospective study suggested that severe skin rash induced by imatinib can be managed by systemic steroid without interruption or dose reduction of imatinib. This phase II study was conducted to evaluate the efficacy and safety of systemic steroid in GIST patients with imatinib-associated severe skin rash. **Methods:** Between October 2014 and March 2016, 29 patients were enrolled and treated with oral prednisolone for imatinib-associated severe skin rash. Severe skin rash was defined as grade 3 skin rash or grade 2 skin rash with pruritus. Prednisolone was started on 30mg daily for 3 weeks, and if skin rash is controlled, then steroid was tapered over 12 weeks. The primary endpoint was treatment success rate (TSR). Treatment success was defined as maintaining imatinib without persistence or recurrence of skin rash requiring 1) additional systemic steroid, or 2) interruption or dose reduction of imatinib. **Results:** Of the 29 patients enrolled, 16 patients (55.2%) received imatinib in adjuvant setting, and 13 (44.8%) in palliative setting. The median age was 61 years (range, 31-77). Eleven patients (37.9%) were male. Twenty-two patients (75.8%, TSR) were treated successfully, 2 (6.9%) were evaluated as treatment failures, and 5 (17.2%) were not evaluable. With a median follow-up of 21.5 months (range, 16.2-27.8), 74.2% of patients could maintain imatinib dose without recurrence of skin rash for 2 years. Median dose intensity or compliance of steroid and imatinib was 100%. No one experienced recurrence or disease progression during follow-up. All toxicities associated with systemic steroid therapy were evaluated. One patient who had myelodysplastic syndrome experienced Pneumocystis pneumonia. Otherwise, steroid was well tolerated. **Conclusions:** This study demonstrated that systemic steroid treatment can effectively control severe skin rash and minimize interruption or dose reduction of imatinib in GIST patients with imatinib-associated severe skin rash.

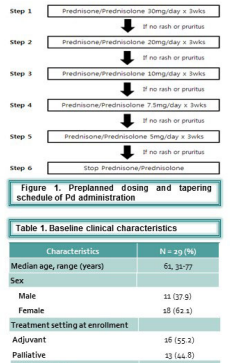

Figure 1. Preplanned dosing and tapering schedule of Pd administration

Table 1. Baseline clinical characteristics

Characteristics	N = 29 (%)
Median age, range (years)	61, 31-77
Sex	
Male	11 (37.9)
Female	18 (62.1)
Treatment setting at enrollment	
Adjuvant	16 (55.2)
Palliative	13 (44.8)
Dose of imatinib	
300 mg/day*	2 (6.9)
400 mg/day	26 (89.7)
600 mg/day**	1 (3.4)
Grade of skin rash	
2	6 (20.7)
3	23 (79.3)

Duration of imatinib use before skin rash development	
Median, Days (range)	41 (0 – 330)
Duration of skin rash before starting Pd administration	
Median, Days (range)	21 (3 - 86)
Blood eosinophil count	
Median, /μL (range)	1059 (10-4025)
< 500 /μL	7 (24.1)
≥ 500 /μL	22 (75.9)

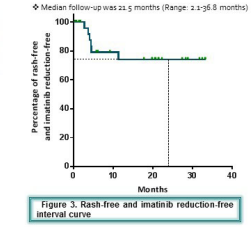

Figure 3. Rash-free and imatinib reduction-free interval curve

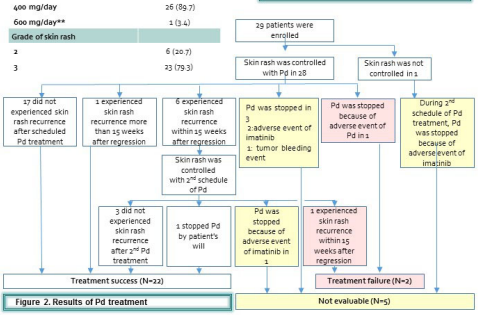

Figure 2. Results of Pd treatment

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Pathological and prognostic impacts of FGFR2 overexpression in stomach cancer

한림대학교 강남성심병원

*이상현, 김형수, 김정한

Background/Aims: Fibroblast growth factor receptor 2 (FGFR2) protein expression by immunohistochemistry (IHC) has been reported in up to 60% of patients with gastric cancer (GC). However, the clinical impact of high FGFR2 expression has not been consistent among studies. We conducted this meta-analysis to evaluate the pathological and prognostic significance of FGFR2 overexpression in patients with GC. **Methods:** A systematic computerized search of the electronic databases including PubMed, PMC, EMBASE, and Web of Science (up to June 2018) was performed. From eleven studies, 4,503 patients were included in the pooled analyses of odds ratios (ORs) with 95% confidence intervals (CIs) for pathological features and hazard ratios (HRs) with 95% CIs for overall survival according to the FGFR2 expression status. **Results:** Compared with tumors harboring low FGFR2 expression, GCs with FGFR2 overexpression showed deeper depth of invasion (pT3-4) (OR=2.63, 95% CI: 1.70-4.06, p<0.0001), higher rate of lymph node metastasis (OR=1.93, 95% CI: 1.41-2.62, p<0.0001), and more advanced stage (III-IV) (OR=1.78, 95% CI: 1.07-2.96, p=0.03). In addition, patients with FGFR2-overexpressed GC showed significantly worse survival than those with FGFR2-low tumor (HR=1.41, 95% CI: 1.25-1.58, p<0.00001). **Conclusions:** In conclusion, this meta-analysis indicates that FGFR2 overexpression is associated with poor pathological features and prognosis in patients with GC.

Figure 2: Forest plots of odds ratios for pT (A), LN metastasis (B), and stage (C).

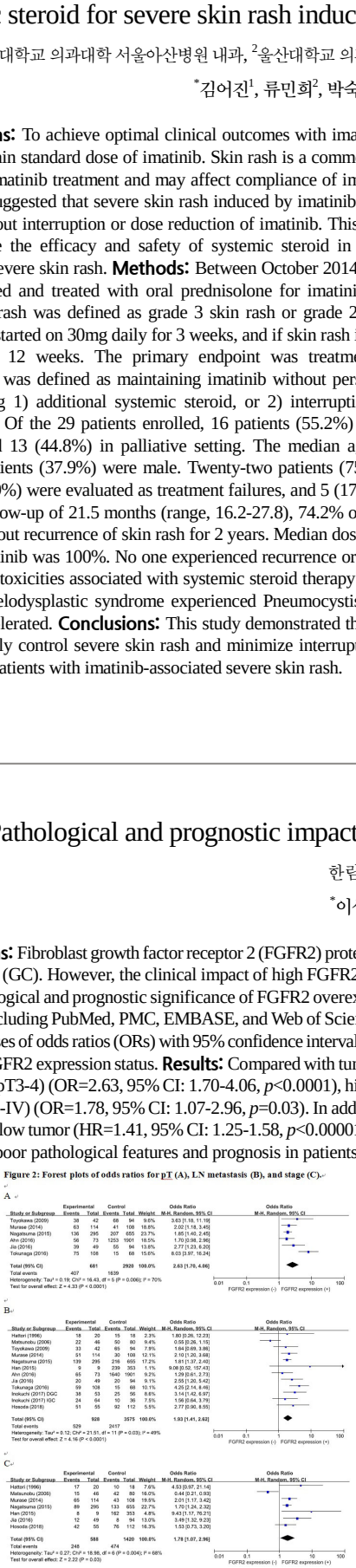

Table 1. Summary of the eleven included studies

First author (year) [ref]	Country	Inclusion period	Stage	No. of patients	Methods, antibody	Interpretation of IHC staining (Cut-off for FGFR2 overexpression)	High GFR2 expression (%)	OR for pT3-4 (95% CI)	OR for LN metastasis (95% CI)	OR for stage (III-IV) (95% CI)	HR for OS (95% CI)
Hattori (1996) [23]	Japan	1990-1991	I-IV	38	IHC with whole slides; Anti-human K-sam IgM 2	NA	20 (52.6%)	NA	1.80 (0.26-12.2); P = 0.32	4.53 (0.97-21.1); P = 0.091	1.73 (0.83-3.68); p = 0.155
Matsusoku (2006) [24]	Japan	1994-1999	I-IV	136	IHC with whole slides; Rabbit anti-KGFR PoAb	Positive staining in more than 10% of tumor cells	46 (66.5%)	NA	0.55 (0.26-1.15); NS	0.44 (0.21-0.93); p = 0.0348	0.87 (0.49-1.55); p = 0.4478
Toyokawa (2009) [25]	Japan	NA	II-IV	136	IHC with whole slides; Rabbit anti-K-sam PoAb	Positive when tumor cells at the invading front >25% were stained more strongly than normal epithelium in the same sample	42 (30.9%)	3.63 (1.18-11.2); p = 0.018	1.64 (0.69-3.88); p = 0.258	NA	1.92 (1.32-2.80); p = 0.0007
Murase (2014) [26]	Japan	2003-2006	I-IV	222	IHC with TMA; Rabbit anti-FGFR2 PoAb	Intensity: 0, no staining; 1, weak; 2, moderate; 3, strong; Percentage of stained tumor cells: 0, no staining; 1, <20%; 2, ≥20 to ≤50%; 3, >50% of tumor cells; (High FGFR2 expression: intensity score + percentage score ≥4)	114 (51.4%)	2.02 (1.18-3.43); p = 0.011	2.10 (1.20-3.68); p = 0.011	2.01 (1.17-3.42); p = 0.012	1.32 (0.77-2.24); p = 0.31
Nagatsuma (2015) [27]	Japan	2003-2007	I-IV	950	IHC with TMA; Rabbit anti-FGFR2 PoAb (sc-122)	Intensity: 0, no staining; 1, faint staining; 2, weak to moderate staining; 3, strong staining; 0, nuclear and cytoplasmic staining in <10% of cells; 1+, staining with intensity 1 in ≥10% to <50%; 2+, staining with intensity 2 in ≥50% to <10%; 3+, staining with intensity 3 in ≥10% (High FGFR2 expression: 2+ and 3+)	295 (31.0%)	1.81 (1.40-2.45); p < 0.001	1.81 (1.37-2.40); p < 0.001	1.70 (1.24-2.32); p < 0.001	1.48 (1.07-2.06); p = 0.018
Han (2015) [28]	Korea	2005	I-IV	362	IHC with TMA; Anti-FGFR2b MoAb (TPIC-D)	0 or 1, no or faint staining or <10% of cells; 2+, weak to moderate staining in ≥10% 3+, strong complete membranous staining in ≥10% (High FGFR2 expression: 2+ or 3+)	9 (2.5%)	NA	9.08 (0.52-157); p = 0.062	9.43 (1.17-76.2); p = 0.036	1.87 (0.91-3.86); P = 0.091
Ahn (2016) [29]	Korea	1996-2006	I-IV	1071	IHC with TMA; Primary FGFR2b Ab (TPIC-D)	Intensity: 1+, cytoplasmic or membranous staining under x 40 magnification; 2+, staining in ≥10 or x20 magnification; 3+, strong staining in ≥4 magnification; (High FGFR expression: intensity score x percentage of stained tumor cells ≥150)	73 (3.7%)	1.70 (0.98-2.94); p = 0.058	1.29 (0.61-2.73); p = 0.064	NA	1.84 (1.03-3.26); p = 0.038
An (2016) [30]	China	2011-2012	I-III	143	IHC with whole slides; Rabbit antihuman FGFR2 Ab (ab10648)	Intensity: 0, no staining; 1, weak staining; 2, moderate staining; 3, strong staining; Percentage of positive cells: 0, 0% positive; 1, <10% positive; 2, 10%~50% positive; 3, >50% positive; (High FGFR2 expression: intensity score + percentage score ≥3)	49 (34.3%)	2.77 (1.24-6.20); p = 0.018	2.35 (1.20-5.42); p < 0.001	1.49 (1.32-0.23); p < 0.001	1.91 (1.22-3.11); p < 0.005
Tokunaga (2016) [31]	Japan	2000-2014	I-IV	176	IHC with whole slides; Mouse anti-FGFR2 MoAb (ab10333)	Intensity: 0, no staining; 1, weak staining, incomplete membranous staining; 2, moderate staining, complete membranous staining; 3, strong staining; (High FGFR2 expression: ≥2)	108 (61.4%)	8.03 (3.97-16.2); p < 0.001	4.25 (2.34-8.46); p < 0.001	NA	1.26 (1.07-1.49); p = 0.007
Inokuchi (2017) [32]	Japan	2003-2007	I-IV	Diffuse (109); Intestinal (100)	IHC with whole slides, Rabbit anti-FGFR2 PoAb (sc-122)	Intensity: 0, no staining; 1, weak positive; 2, moderate or strong; Percentage: 1, <10%; 1, 10% to 50%; 2, <50% or 64 (64%) tumor cells; (High FGFR2 expression: ≥3)	53 (48.6%); 64 (64%)	NA	3.14 (1.42-6.97); p = 0.007; 1.56 (0.64-3.79); p = 0.33	NA	1.50 (0.69-3.1); p = 0.32; 1.55 (0.52-4.60); p = 0.43
Hosoda (2018) [33]	Japan	2000-2010	II-III	172	IHC with whole slides; Mouse anti-FGFR2 MoAb	0, staining in <10% of tumor cells; 1+, faint cytoplasmic and/or nuclear staining in ≥50%; 2+, weak to moderate staining in ≥ 10%; 3+, strong staining in ≥50%; (High FGFR2 expression: 3+)	55 (31.9%)	NA	2.77 (0.90-8.55); p = 0.099	1.53 (0.73-3.20); p = 0.283	1.25 (0.73-2.09); p = 0.411

FGFR, fibroblast growth factor receptor; KGFR, keratinocyte growth factor receptor; IHC, immunohistochemistry; TMA, tissue microarray; MoAb, monoclonal antibody; PoAb, polyclonal antibody; OR, odds ratio; HR, hazard ratio; CI, confidence interval; OS, overall survival; LN mets, lymph node metastasis; NA, not available