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Intensity-Adjusted Salvage Chemotherapy Plus FLT3-Inhibitor Gilteritinib in Relapsed/Refractory Acute Myeloid Leukemia with Mutated FLT3-ITD/TKD (SAPPHIRE-G)

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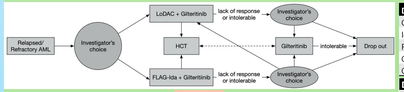
Background

The addition of cytarabine, daunorubicin, idarubicin, or azacitidine to gilteritinib potentiated apoptosis. Gilteritinib combined with cytarabine, daunorubicin, idarubicin, or azacitidine, inhibited anti-apoptotic protein expression in MV4-11 cells. These preclinical trials suggest the synergistic effect of FLT3 inhibitors with chemotherapeutic agents and needs for further investigation. Gilteritinib therapy promotes differentiation of leukemic blasts in a sizeable subset of relapsed/refractory (R/R) FLT3 mut acute myeloid leukemia (AML) because differentiated AML cells are more susceptible to chemotherapeutic agents. The addition of idarubicin with FLAG (FLAG- IDA) is a usual salvage chemotherapy in R/R AML. We wanted to know the safety and efficacy of the combination of gilteritinib with salvage chemotherapy. Intensive chemotherapy ineligible patients can benefit with low-dose cytarabine which is one of the salvage chemotherapy for R/R AML.

In this study, we studied the safety and efficacy of the gilteritinib combined with intensity-adjusted salvage chemotherapies in R/R AML patients.

Methods

Inclusion criteria were R/R FLT3-ITD/TKD mutated AML; No prior exposure to Gilteritinib (prior exposure of other FLT3-inhibitors was permitted including quizartinib or midostaurin); Mean QTcF interval of ECG of 480 ms or shorter. Patients must be 19 years of age or older. The salvage chemotherapy was decided by the investigator's choice according to intensive chemotherapy eligibility; FLAG-IDA + gilteritinib for intensive chemotherapy eligible patients, or low-dose cytarabine + gilteritinib for intensive chemotherapy ineligible patients. Gilteritinib was combined by intensity-adjusted salvage chemotherapy in R/R AML. Gilteritinib was given 120mg daily on D6-D26 for 3 weeks (D4 to D24 during FLAG-Ida consolidation). When LoDAC was chosen as the salvage regimen, the Gilteritinib starting day was day 11 for 3 weeks. All available patients received hematopoietic cell transplantation (HCT).
Primary end point was complete remission (CR) rate in intention to treat group (ITTG). Secondary end points were composite CR (cCR; CR+CRh+CRi) and overall response (CR+CRh+CRi+PR) in per-protocol group (PPG), safety evaluation in safety group (SG), progression-free survival (PFS), overall survival (OS).



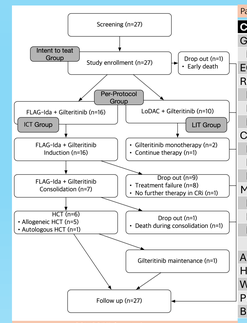
Study design

Drug	Dose	Route	Infusion time	D1	D2	D3	D4	D5	D6-26
G-CSF	400μg/m²	SC/IV		√	√	√	√	√	
Idarubicin	5 mg/ m²	IV	Over 30min	√	√	√			
Fludarabine	30mg/m²	IV	Over 30min	√	√	√	√	√	
Cytarabine	2g/m²	IV	4h (4h before fludarabine)	√	√	√	√	√	
Gilteritinib	120mg qd	PO	-						√

Drug	Dose	Route	Infusion time	D1-10	D11-31
Cytarabine	20mg	SC	q12hr	√	
Gilteritinib	120mg	PO	qd		√

Results

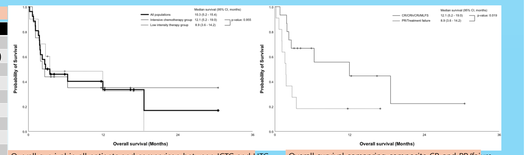
Total 27 patients (ITTG) were enrolled in this study. One patient did not receive any study treatment because of early death prior to study drug administration. Therefore 26 patients (PPG) received the planned salvage therapy. The median age was 63 years (range,). Male patients were 15/27 (55.6%). Eight (29.6%) were primary refractory AML, 16 were first relapsed AML and 3 patients were multiple relapsed AML at the time of study enrollment. Sixteen (59.3%) patients had received intensive chemotherapy (ICTG; FLAG-Ida + Gilteritinib) and 10 (37.0%) patients had received low intensive therapy (LITG; low-dose cytarabine + Gilteritinib) and 1 patient did not receive any planned therapy. In ITTG, CR rates were 10/27 (37.0%). Composite CR (cCR; CR+CRh+CRi) rate was 15/27 (55.6%) and overall response rate (ORR) including cCR and PR was 16/27 (59.3%). In PPG, CR, cCR and ORR were 10/26 (38.5%), 15/26 (57.7%) and 17/26 (61.5%), respectively. When considering ICTG only, CR, cCR and ORR were 8/16 (50.0%), 11/16 (68.8%) and 11/16 (68.8%), respectively. When considering LITG only, CR, cCR and ORR were 2/10 (20.0%), 4/10 (40.0%) and 5/10 (50.0%), respectively. When comparing first relapsed AML and refractory/multiple relapsed AML in PPG (n=26), CR rate (p=0.530), cCR rate (p=0.599) and ORR (p=0.428) were similar. Also, when comparing ICTG and LCTG, CR rate (p=0.218), cCR rate (p=0.228) and ORR (p=0.339) showed no statistically significant differences. Five patients (19.2%) and 1 patient (3.8%) could be bridged to allogeneic or autologous hematopoietic cell transplantation, respectively. Median overall survival (OS) in PPG, ICTG and LITG were 2.8, 2.2, and 3.1 months, respectively. Even though median survival was short, 35% in ICTG showed long-term survival. Median OS in patients who had achieved ORR were 12.0 months.



CONSORT for study process

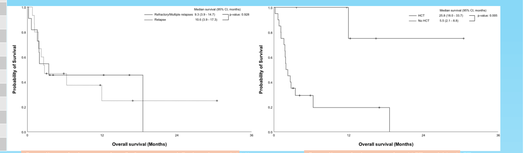
Patients' characteristics

Characteristics	No. patients (%)
Gender	
Male/Female	15 (55.6)/12 (44.4)
ECOG 0-1	13 (48.1)
Relapsed/Refractory status	
Primary refractory	8 (29.6)
Early relapse	16 (59.3)
Multiple relapses	3 (11.1)
Cytogenetic risk	
Favorable	4 (14.8)
Intermediate	14 (51.9)
High	9 (33.3)
Molecular abnormalities	
FLT3-ITD^{mut}	25 (92.6)
FLT3-TKD^{mut}	3 (11.1)
NPM1^{mut}	7 (25.9)
	Median (range)
Age	63 (27-89)
Hemoglobin (g/dL)	9.2 (7.1-16.9)
WBC (/μL)	12.6 (0.3-67.0)
Platelet (/μL)	40.5 (8.0-225.0)
Bone marrow blast (%)	54.0 (6.2-92.4)



Overall survival in all patients and comparison between ICTG and LITG.

Overall survival comapring composite CR and PR/failure.



Overall survival comapring Refractory and Early relapsed AML.

Overall survival comapring HCT and No HCT

Conclusion

Gilteritinib combined with chemotherapy in R/R AML showed reasonable efficacy not only for chemotherapy-eligible patients who had received intensive chemotherapy but also for chemotherapy-ineligible patients who had received low-dose cytarabine.

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