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Quizartinib for Treatment of Patients with Relapsed/Refractory FMS-like Tyrosine Kinase 3 (FLT3)-Internal Tandem Duplication (ITD) Acute Myeloid Leukaemia (AML)

Keywords: FLT3-inhibitor, relapsed or refractory acute myeloid leukemia, anti-neoplastic agent, tyrosine kinase inhibitor

SUMMARY OF TECHNOLOGY

Quizartinib is an investigational oral anti-cancer medication for the treatment of adult patients with relapsed/refractory AML, who is FLT3-ITD positive.

In normal bone marrow, FLT3 receptor undergoes conformational change, dimerizing and becoming autophosphorylated, triggering downstream pathways that promote haematopoietic expansion by stimulating cell proliferation and inhibiting apoptosis.

In AML, FLT3 is expressed at high levels in 70 - 100% of the cases. The most common of these mutations, FLT3-ITD, is an in-frame duplication of variable length of FLT3 exons 14 and 15, which occurs in about 20 - 30% of adult AML. FMS-like Tyrosine Kinase 3 - Internal Tandem Duplication (FLT3-ITD) disrupt the negative regulatory function of the juxtamembrane domain, resulting in constitutive tyrosine kinase activation and also signaling pathway downstream of FLT3. Subsequently it generates high white blood cell count, and increases bone marrow and blast percentage (leukemogenesis). (As seen in Figure 1)

This agent selectively inhibits Class III receptor tyrosine kinases, including FMS-related tyrosine kinase 3 (FLT3/STK1), colony-stimulating factor 1 receptor (CSF1R/FMS), stem cell factor receptor (SCFR/KIT) and platelet-derived growth factor receptors (PDGFRs). The FLT3 inhibition is necessary to affect blasts within the marrow, and it needs to be sustained to induce apoptosis. While inhibition of the mutant receptor in cell lines or AML blasts in suspension culture with a FLT3 tyrosine kinase inhibitor (TKI) results in apoptosis, blasts within the marrow are more resistant to this therapy, in part because of local production of FL and other cytokines.

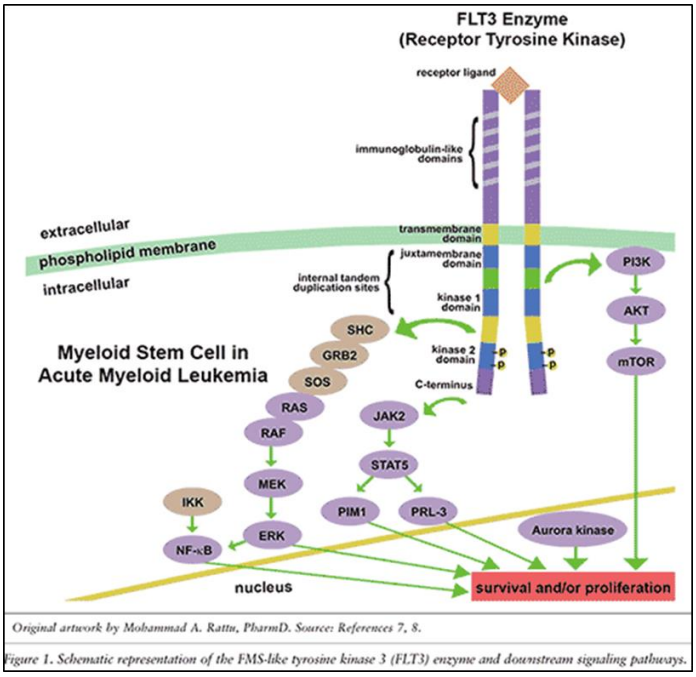

Figure 1: The process of leukemogenesis.

U.S. Food and Drug Administration (FDA) Grants Priority Review for Daiichi Sankyo's New Drug Application for FLT3 Inhibitor Quizartinib for Treatment of Patients with Relapsed/Refractory FLT3-ITD AML on 21st November 2018. However, FDA Oncologic Drugs Advisory Committee had voted against approving the NDA on the 14th May 2019.

Daiichi Sankyo Company Limited has submitted marketing authorization application to European Medicines Agency (EMA) on 6 November 2018. The company announced that EMA has validated and granted accelerated assessment for Quizartinib.

The Ministry of Health, Labor and Welfare (MHLW) of Japan has recently approved VANFLYTA® (quizartinib) on 18 June 2019.

INNOVATIVENESS

Novel, completely new	√
Incremental improvement of the existing technology	
New indication of an existing technology	

DISEASE BURDEN

Acute myeloid leukaemia (AML) is characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in haematopoietic insufficiency (granulocytopaenia, thrombocytopaenia, or anaemia), with or without leukocytosis.[1]

The American Cancer Society estimates that for 2019, there will be about 21,450 new cases of acute myeloid leukaemia (AML) and mostly will be in adults. The society also estimates about 10,920 dies from AML.[2] Acute myeloid leukaemia predominantly affects patients who are in their sixth decade of life or older, with an average age of 66 years at diagnosis. The lifetime risk of AML for men is about one in 227, while it is about one in 278 for women (i.e., men are more likely to be diagnosed with AML). The 5-year relative survival rate of AML is 24%, which has improved slightly from the 21.7% observed between 1996 and 2002.[2]

FMS-like Tyrosine Kinase 3 (FLT3) gene mutations is one of the most common genetic abnormalities in AML. The most common FLT3 mutation is FLT3-ITD which affects approximately one in four patients with AML. FMS-like Tyrosine Kinase 3 - Internal Tandem Duplication is a driver mutation that presents with high leukaemic burden and has poor prognosis and a significant impact on disease management for patients with AML.

FMS-like tyrosine kinase 3 internal tandem duplications (FLT3-ITD) in acute myeloid leukaemia (AML) are associated with early relapse after standard chemotherapy and poor survival.

CURRENT OPTIONS FOR PATIENTS

The treatment of adult AML usually has two phases which consist of remission induction therapy and post-remission therapy. Currently, there are four types of standard treatment which includes chemotherapy, radiation therapy, chemotherapy with stem cell transplant and other drug therapy (arsenic trioxide and all-trans retinoic acid (ATRA). At present, targeted therapy using monoclonal antibodies are being tested in clinical trials.

The treatment for relapsed AML involves a repeat course of the 7-and-3 protocol. In this protocol, cytarabine (Cytosar, Ara-C) is given continuously for seven days with an anti-tumour antibiotic given for three days. The anti-tumour antibiotics used in this protocol include daunorubicin (Cerubidine), doxorubicin (Adriamycin), idarubicin (Idamycin), and/or mitoxantrone (Novantrone). [3]

Other types of chemotherapy that may be offered for relapsed or refractory AML are high-dose cytarabine (HDAC) alone or in combination with an anti-tumour antibiotic etoposide (Vepesid, VP-16), cytarabine and mitoxantrone (Novantrone) or high-dose etoposide and cyclophosphamide (Cytoxan, Procytox) or FLAG – fludarabine (Fludara), cytarabine and granulocyte colony-stimulating factor (G-CSF).

POTENTIAL IMPACT OF TECHNOLOGY

Systematic search from MEDLINE, Embase, Cochrane Library and EUROScan database identifies one phase 2 study and one phase 3 clinical trials.

Efficacy

An open label, single-arm, multicenter phase two study recruited 333 patients from two predefined, independent cohorts. The first cohort consisted of patients aged 60 years or older with relapsed or refractory AML within one year after first-line therapy. Whereas the second cohort consisted of those who were 18 years or older with relapsed or refractory disease following salvage chemotherapy or haemopoietic stem cell transplantation. All patients received quizartinib once daily as an oral solution. The initial 17 patients received 200 mg per day but the QTcF interval was prolonged for more than 60 ms above baseline in some of these patients. Subsequently, doses were amended for all patients to 135 mg per day for men and 90 mg per day for women. In cohort 1 (n= 157), 63 of 112 FLT3-ITD-positive patients and 16 of 44 FLT3-ITD-negative patients achieved composite complete remission, with three FLT3-ITD-positive patients and two FLT3-ITD-negative patients achieving complete remission. In cohort 2 (n= 176), 62 of 136 FLT3-ITD-positive patients achieved composite complete remission with five achieving complete remission, whereas 12 of 40 FLT3-ITD-negative patients achieved composite complete remission with one achieving complete remission.[4]

According to QuANTUM-R which is a global, phase three, randomised, controlled trial (NCT02039726), involving patients aged more than 18 years with FLT3-ITD–mutated AML who were refractory to or relapsed (with duration of first complete remission [CR1] of six months or less) after standard AML therapy, with and without haematopoietic stem cell transplantation (HSCT). The participants were randomised 2:1 to receive Quizartinib (60-mg, with a 30-mg lead-in) or investigator's choice salvage chemotherapy (SC), which was selected prior to randomisation. Allowed SC regimens were low dose cytarabine (LoDAC); mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC); or fludarabine, cytarabine, and granulocyte-colony stimulating factor (GCSF) with idarubicin (FLAG-IDA). Up to 2 cycles of MEC or FLAG-IDA were permitted; Quizartinib and LoDAC were given until lack of benefit, unacceptable toxicity, or HSCT. Prior therapy with FLT3i (except the multikinase inhibitor, midostaurin) was not allowed. Patients receiving HSCT in the Quizartinib arm were allowed to resume Quizartinib therapy following transplant. The primary endpoint was overall survival (OS). A total of 367 patients were randomised to Quizartinib (n=245) and SC (n=122 [LoDAC, n=29; MEC, n=40; FLAG-IDA, n=53]). Median follow-up was 102.4 weeks at study analysis. The result indicated that OS hazard ratio of Quizartinib relative to SC was 0.76 (95% CI: 0.58, 0.98; stratified log-rank test, 1-sided P=0.0177). Median OS was 27 weeks (95% CI: 23.1, 31.3) and 20.4 weeks (95% CI: 17.3, 23.7) for patients treated with Q and SC, respectively. Estimated survival probability at 52 weeks was 27% for the Q arm and 20% for the SC arm. [5]

Safety

According to the Phase 2 trial, across both cohorts (ie, the intention-to-treat population of 333 patients), the occurrence of grade 3 or worse treatment-related treatment-emergent adverse events was 5% which were febrile neutropaenia (23%), anaemia (23%), thrombocytopaenia (12%), QT interval corrected using Fridericia's formula (QTcF) prolongation (10%), neutropaenia (9%), leucopaenia (7%), decreased platelet count (6%), and pneumonia (5%). Serious adverse events occurring in 5% or more of patients were febrile neutropaenia (38%; 76 were treatment related), acute myeloid leukaemia progression (22%), pneumonia (12%; 14 treatment related), QTcF prolongation (10%; 32 treatment related), sepsis (8%; eight treatment related), and pyrexia (5%; nine treatment related). Notable serious adverse events occurring in less than 5% of patients were torsades de pointes (one [<1%]) and hepatic failure (two [1%]). In total, 125 of 333 patients (38%) died within the study treatment period, including the 30-day follow-up. Eighteen (5%) patients died because of an adverse event considered by the investigator to be treatment related (ten [6%] of 157 patients in cohort 1 and eight [5%] of 176 in cohort 2).

According to QuANTUM-R, rates of treatment emergent adverse events were comparable between the two arms. Only two patients discontinued Quizartinib due to QTcF prolongation. No events of torsades de pointes were reported. The safety profile appears consistent with that observed at similar doses in the Quizartinib program. The most common adverse events (>30% in any Grade) in patients treated with quizartinib versus chemotherapy, respectively, included nausea (48 versus 42 %), thrombocytopaenia (39 versus 34 %), fatigue (39 versus 29 %), musculoskeletal pain (37 versus 28 %), pyrexia (38 versus 45 %), anaemia (37 versus 32 %), neutropaenia (34 versus 26 %), febrile neutropaenia (34 versus 28 %), vomiting (33 versus 21 %) and hypokalaemia (32 versus 28 %). The most common adverse events Grade ≥3 (occurred in >10% of patients) were thrombocytopaenia (35 versus 34%), anaemia (30 versus 29%), neutropaenia (32 versus25%), febrile neutropaenia (31 versus 21%), leukopenia (17 versus 16%), sepsis or septic shock (16 versus 18%), hypokalaemia (12 versus 9%) and pneumonia (12 versus 9 %). There were no reported events of Grade 4 QTcF prolongation (Torsade de Pointes, sudden death or cardiac arrest) in the quizartinib arm.

Cost

There was no retrievable evidence on the cost of the drug. Comparatively, most of the current chemotherapy drugs are costly. Among the price of chemotherapy drug used for treatment of relapsed AML are daunorubicin (Cerubidine) estimated to be USD 163.01 (~RM682) per vial, doxorubicin (Adriamycin) with the cost of USD 64.8 (~RM271) per vial, idarubicin (Idamycin) with USD 60.0 (~RM251) and mitoxantrone (Novantrone) with it’s estimation of price of USD 1649.32 (~RM6,901.58) per vial.

In conclusion, quizartinib showed potential to be effective for the treatment of patients with relapsed/refractory FLT3-ITD AML. However, the cardiac complications seen in the patients in the mentioned studies needs further evaluation. The cost-effectiveness of Quizartinib should also be considered.

EVIDENCE

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