THINK FLT3 ONE MORE TIME

AML: DEVASTATING

WITH A FLT3 MUTATION: DISASTROUS

IN PATIENTS WITH AML,

A *FLT3-ITD* mutation drives progression and may lead to lower patient survival.[1-3]

Explore the clinical impact of FLT3 at

thinkflt3.co.uk

Prescribing information for: XOSPATA™ ▼ 40 mg film coated tablets (gilteritinib). **Indications:** Gilteritinib is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation. **Posology and administration:** Treatment with gilteritinib should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Before taking gilteritinib, relapsed or refractory AML patients must have confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test. The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) orally once daily, with or without food, swallowed whole with water and should not be broken or crushed. Gilteritinib should be administered at about the same time each day. See *Special warnings and precautions for use* section on tests to be conducted prior to initiation e.g. blood chemistries, ECG & pregnancy test. Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response. In the absence of a response (patient did not achieve a composite complete remission (CRc) after 4 weeks of treatment), the dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted. Gilteritinib may be re-initiated in patients following haematopoietic stem cell transplantation (HSCT), Planned HSCT: Interrupt treatment one week prior to administration of the conditioning regimen for HSCT. Treatment can be resumed 30 days after HSCT if engraftment was successful, the patient did not have grade ≥2 acute graft versus host disease and was in CRc. Elderly: No dose adjustment is required in patients ≥65 years of age. Gilteritinib is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment. Please refer to SPC, section 4.2 for full instructions for use in hepatic & renal impairment. Paediatric population: The safety and efficacy of gilteritinib in children aged below 18 years has not yet been established. No data are available. Due to in vitro binding to $5HT_{2B}$, there is a potential impact on cardiac development in patients less than 6 months of age. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. **Special warnings and precautions for use:** Differentiation syndrome: Gilteritinib has been associated with differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and clinical findings of differentiation syndrome include fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with haemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, gilteritinib should be interrupted until signs and symptoms are no longer severe. Corticosteroids can be tapered after resolution of symptoms and should be administered for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2 or lower. Posterior reversible encephalopathy syndrome: There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving gilteritinib. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of gilteritinib in patients who develop PRES is recommended. Prolonged QT interval: Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT interval). QT prolongation can be observed in the first three months of treatment with gilteritinib. Therefore, ECG should be performed prior to initiation of treatment, on day 8 and 15 of cycle 1, and prior to the start of the next three subsequent months of treatment. Caution is warranted in patients with relevant cardiac history. Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during gilteritinib treatment. Gilteritinib should be interrupted in patients who have a QTcF >500 msec.The decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on careful consideration of benefits and risks. Resume gilteritinib at a reduced dose (from 120 mg to 80 mg or from 200 mg to 120 mg) when QTcF interval returns to within 30 msec of baseline or ≤480 msec. Patients with QTcF interval increase by >30 msec on day 8 of cycle 1 should have a further ECG on day 9; if QTcF increase is confirmed gilteritinib dose should be reduced to 80 mg. If gilteritinib is re-introduced at a reduced dose, ECG should be performed after 15 days of dosing, and prior to the start of the next three subsequent months of treatment. In clinical studies, 12 patients had QTcF >500 msec. Three patients interrupted and re-initiated treatment without recurrence of QT prolongation. Pancreatitis: There have been reports of pancreatitis. Patients who develop signs and symptoms suggestive of pancreatitis should be evaluated and monitored. Gilteritinib should be interrupted and can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg) when the signs and symptoms of pancreatitis have resolved. Toxicity: If the patient experiences other Grade 3 or higher toxicity considered related to treatment, interrupt treatment until the toxicity resolves or improves to Grade 1. If deemed clinically appropriate gilteritinib can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg). Interactions: Co-administration of CYP3A/P-gp inducers may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of gilteritinib with strong CYP3A4/P-gp inducers should be avoided. Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A,P-gp and/or breast cancer resistant protein (BCRP) (such as, but not limited to, voriconazole, itraconazole, posaconazole and clarithromycin) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A, P-gp and/or BCRP activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicities during administration of gilteritinib. Gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. Therefore, concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient. Embryofoetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus. Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with gilteritinib and to use effective contraception during treatment with gilteritinib and for at least 6 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of gilteritinib. **Interactions:** Gilteritinib is primarily metabolised by CYP3A enzymes, which can be induced or inhibited by a number of concomitant medicinal products. See Special Warnings and Precautions for Use section above for further information on this and the effects of gilteritinib on products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. *Gilteritinib as an inhibitor or inducer:* gilteritinib is not an inhibitor or inducer of CYP3A4 or an inhibitor of MATE1 *in vivo*. Gilteritinib is an inhibitor of P-gp, BCRP and OCT1 (organic cation transporter 1) *in vitro*. As no clinical data is available, it cannot be excluded that gilteritinib could inhibit these transporters at a therapeutic dose. Caution is advised during co-administration of gilteritinib with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, methotrexate, rosuvastatin) and OCT1 (e.g., metformin). **Fertility, pregnancy and lactation:** Pregnancy: Gilteritinib is not recommended during pregnancy and in women of childbearing potential not using effective contraception. See Special Warnings and Precautions for Use section above for information on pregnancy testing and contraception. Breastfeeding: Breastfeeding should be discontinued during treatment with gilteritinib and for at least two months after the last dose. Fertility: There are no data on the effect of gilterinitib on human fertility. **List of adverse reactions:** *Prescribers should consult the SPC for full information on adverse events* **List of adverse reactions:** Very common (≥1/10): Dizziness, Hypotension, Cough, Dyspnoea, Diarrhoea, Nausea, Constipation, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatine phosphokinase increased, Blood alkaline phosphatase increased, Pain in extremity, Arthralgia, Myalgia, Fatigue, Peripheral oedema and Asthenia. Common (≥1/100 to <1/10): Anaphylactic reaction, Electrocardiogram QT prolonged, Pericardial effusion, Pericarditis, Cardiac failure, Differentiation syndrome, Musculoskeletal pain, Acute kidney injury and Malaise. Serious adverse reactions: The most frequent serious adverse reactions noted from evaluation of 319 patients with relapsed or refractory AML who have received at least one dose of 120 mg gilteritinib were acute kidney injury, diarrhoea, ALT increased, dyspnea, AST increased and hypotension. Other clinically significant serious adverse reactions included differentiation syndrome, electrocardiogram QT prolonged and posterior reversible encephalopathy syndrome. **Overdose:** There is no known specific antidote for gilteritinib. In the event of an overdose, treatment should be stopped. Patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated, taking into consideration the long half-life estimated at 113 hours. **Cost (excluding VAT):** United Kingdom (UK): XOSPATA 40 mg film-coated tablets x 84: £14,188.00. **Legal classification:** POM. **Marketing authorisation number:** Great Britain (GB): PLGB 00166/0425. Northern Ireland NI: EU/1/19/1399/001. **Marketing authorisation holder:** GB: Astellas Pharma Ltd., 300 Dashwood Lang Road, Bourne Business Park, Addlestone, United Kingdom, KT15 2NX. NI: Astellas Pharma Europe B.V. Sylviusweg 62, 2333 BE Leiden, The Netherlands. **Date of preparation:** March 2023. **Document number:** MAT_UK_XOS_2023_00039. **Further information available from:** Astellas Pharma Ltd., Medical Information: 0800 783 5018.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018.

AML=acute myeloid leukemia; FLT3=FMS-like tyrosine kinase 3; ITD=internal tandem duplication.

References: 1. Chevallier P, et al. Leukemia 2011;25(6):939-44. **2.** Gale RE, et al. Blood 2008;111(5):2776-84. **3.** Smith CC, et al. Nature 2012;485(7397):260-3.

astellas

MAT-UK-XOS-2023-00023 | March 2023

British Journal of Haematology, 1994, **88**, 199–200

SHORT REPORT

Predicting the severity of rhesus alloimmunization: monocyte-mediated chemiluminescence versus maternal anti-D antibody estimation

A. G. S. Buggins, B. Thilaganathan,* H. Hambley and K. H. Nicolaides† *Department of Haematology, and* **Harris Birthright Research Centre for Fetal Medicine, Kings College Hospital Medical School, London*

Received 22 April 1994; accepted for publication 15 June 1994

Summary. Anti-D haemolytic antibody concentration and chemiluminescence (CLT) opsonic index was measured in maternal blood obtained from 20 alloimmunized pregnancies at 17–28 weeks undergoing intrauterine fetal blood sampling for the estimation of fetal haemoglobin concentration. The fetal haemoglobin concentration was significantly associated with the maternal serum CLT opsonic index ($r = -0{\cdot}566$, $P < 0{\cdot}01$) but not with the maternal anti-D concentration ($r = -0{\cdot}329$). The data of this study indicate that measurement of maternal serum CLT opsonic index may be more accurate than anti-D quantification in providing non-invasive prediction of the degree of fetal anaemia.

Keywords: Rh alloimmunization, fetal anaemia, anti-D estimation, monocyte-mediated chemiluminescence.

In the management of red blood cell alloimmunized pregnancies, measurement of haemolytic antibody concentration in maternal blood provides an indirect measure of the severity of the disease. However, there is a poor correlation between fetal haemoglobin concentration deficit and maternal antibody level (Nicolaides & Rodeck, 1992). This study examines whether a more accurate prediction of the severity of the disease can be provided by the monocyte-mediated chemiluminescence test (CLT), which is a functional assay of the interaction between sensitized red blood cells and human mononuclear cells.

PATIENTS AND METHODS

Fetal blood was obtained by cordocentesis in 20 Rh alloimmunized pregnancies at 17–28 weeks gestation. The direct antiglobulin test was positive in all cases and Kleihauer staining showed that all samples contained only fetal red blood cells. The haemoglobin concentration was determined using a Coulter STKR counter (Coulter Electronics, Luton, U.K.).

Maternal blood was obtained by venepuncture immediately before cordocentesis for measurement of serum anti-D concentration (autoanalyser calibrated against the British anti-D working standard 72/229: Marsh *et al*, 1968) and CLT opsonic index. For the latter, a luminol-enhanced chemiluminescence assay was used to measure the metabolic activity of monocytes during erythrophagocytosis. Mononuclear cells from five pooled normal donors were isolated and resuspended in 1:2 RPMI/fetal calf serum:Hanks balanced salt solution (Sigma, Poole, U.K.). The cells were then incubated in a 5% CO_2 atmosphere at 37°C for 2 h. Equal volumes of maternal serum and 5% vol/vol group O red blood cells from a D-positive donor were incubated at 37°C for 1 h. The sensitized red cells were washed three times in phosphate-buffered saline and resuspended at their original concentration. Mononuclear cells and sensitized red blood cells were mixed and then added to 4×10^{-4} M luminol (Sigma). The chemiluminescence response of the monocytes was monitored for 1 h at 37°C in a luminometer (Bio-orbit 1251, Labsystems UK Ltd, Basingstoke). An opsonic index was calculated for each case by dividing the mean chemiluminescence response to sensitized red blood cells by the mean chemiluminescence response to non-sensitized red blood cells.

Correspondence: Professor K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, Kings College Hospital Medical School, Denmark Hill, London SE5 8RX.

RESULTS

The fetal haemoglobin concentration was significantly associated with the maternal serum CLT opsonic index

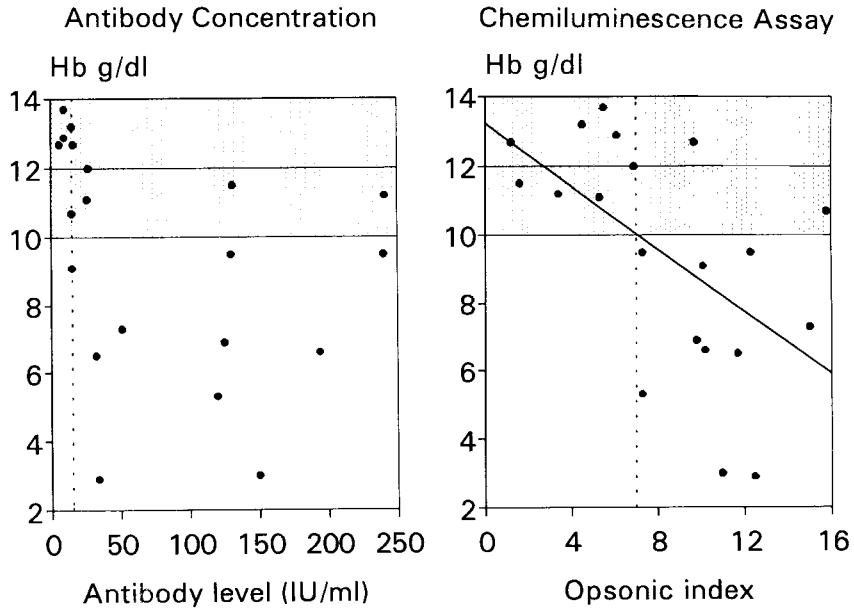

Fig 1. The association between fetal haemoglobin concentration and maternal chemiluminescence opsonic index (left) and anti-D antibody concentration (right). The sloping line represents the regression line. The dotted lines represent the values ($\geqslant 7$ for the CLT opsonic index and $\geqslant 15$ IU/ml for the antibody concentration) above which the fetus could be anaemic.

(Fig 1; $r = -0{\cdot}566$, $P < 0{\cdot}01$) but not with the maternal anti-D concentration (Fig 1; $r = -0{\cdot}329$).

DISCUSSION

The data of this study indicate that measurement of maternal serum CLT opsonic index may be more accurate than anti-D estimation in providing non-invasive prediction of the degree of fetal anaemia. These findings are compatible with the observation that the clinical severity of haemolytic disease of the newborn is best correlated with maternal CLT opsonic index rather than antibody level (Hadley *et al*, 1991; Lucas *et al*, 1993).

Our findings concur with those of the previous report that fetal anaemia is unlikely when the maternal serum anti-D concentration is <15 IU/ml. for levels $\geqslant 15$ IU/ml fetuses may be anaemic but the severity can not be predicted from the antibody concentration (Nicolaides & Rodeck, 1992). In contrast, maternal serum CLT opsonic index provides useful prediction of fetal anaemia; in 10/12 pregnancies with an index of $\geqslant 7$ the fetal haemoglobin concentration was below the fifth centile of the normal range. CLT opsonic index, unlike antibody concentration, provides a measure of the interaction between antibody-coated red blood cells and the reticuloendothelial system.

In the management of red blood cells alloimmunized pregnancies, cordocentesis provides access to the fetal circulation for assessment of haemoglobin concentration and intravascular transfusions. However, this invasive procedure entails at least a 1% risk of fetal death even with experienced operators. Our findings suggest that cordocentesis may be avoided if the maternal serum CLT opsonic index is less than 7.

REFERENCES

Hadley, A.G., Kumpel, B.M., Leader, K.A., Poole, G.D. & Frazer, I.D. (1991) Correlation of serological, quantitative and cell-mediated functional assays of maternal alloantibodies with the severity of haemolytic disease of the newborn. *British Journal of Haematology*, 77, 221–228.

Lucas, G.F., Hadley, A.G., Nance, S.J. & Garratty, G. (1993) Predicting haemolytic disease of the newborn: a comparison of the monocyte monolayer assay and the chemiluminescence test. *Transfusion*, **33**, 484–487.

Marsh, W.L., Nichols, M. & Jenkins, W.J. (1968) Automated detection of blood group antibodies. *Journal of Medical Laboratory Technology*, **25**, 335–342.

Nicolaides, K.H. & Rodeck, C.H. (1992) Maternal serum anti-D antibody concentration and assessment of rhesus alloimmunisation. *British Medical Journal*, **304**, 1155–1156.