Sorafenib

Sorafenib (co-developed and co-marketed by Bayer and Onyx Pharmaceuticals as **Nexavar**),[1] is a kinase inhibitor drug approved for the treatment of primary kidney cancer (advanced renal cell carcinoma), advanced primary liver cancer (hepatocellular carcinoma), and radioactive iodine resistant advanced thyroid carcinoma.

1 Mechanism of action

Sorafenib is a small inhibitor of several tyrosine protein kinases, such as VEGFR, PDGFR and Raf family kinases (more avidly C-Raf than B-Raf).[2][3][4]

(See BRAF (gene)#Sorafenib for details of drug structure interaction with B-Raf.)

Sorafenib treatment induces autophagy,[5] which may suppress tumor growth. However, autophagy can also cause drug resistance.[6]

2 Medical uses

At the current time sorafenib is indicated as a treatment for advanced renal cell carcinoma (RCC), unresectable hepatocellular carcinomas (HCC) and thyroid cancer.[7][8][9][10]

2.1 Kidney cancer

An article in The New England Journal of Medicine, published January 2007, showed that, compared with placebo, treatment with sorafenib prolongs progression-free survival in patients with advanced clear cell renal cell carcinoma in whom previous therapy has failed. The median progression-free survival was 5.5 months in the sorafenib group and 2.8 months in the placebo group (hazard ratio for disease progression in the sorafenib group, 0.44; 95% confidence interval [CI], 0.35 to 0.55; P<0.01).[11] A few reports described patients with stage IV renal cell carcinomas, metastasized to the brain, that were successfully treated with a multimodal approach including neurosurgical, radiation, and sorafenib.[12] This is one of two TGA-labelled indications for sorafenib, although it is not listed on the British Pharmaceutical Benefits Scheme for this indication.[10][13]

2.2 Liver cancer

At ASCO 2007, results from the SHARP trial[14] were presented, which showed efficacy of sorafenib in hepatocellular carcinoma. The primary endpoint was median overall survival, which showed a 44% improvement in patients who received sorafenib compared to placebo (hazard ratio 0.69; 95% CI, 0.55 to 0.87; p=0.0001). Both median survival and time to progression showed 3-month improvements. There was no difference in quality of life measures, possibly attributable to toxicity of sorafenib or symptoms related to underlying progression of liver disease. Of note, this trial only included patients with Child-Pugh Class A (i.e. mildest) cirrhosis. The results of the study appear in the July 24, 2008, edition of The New England Journal of Medicine. Because of this trial Sorafenib obtained FDA approval for the treatment of advanced hepatocellular carcinoma in November 2007.[4]

In a randomized, double-blind, phase II trial combining sorafenib with doxorubicin, the median time to progression was not significantly delayed compared with doxorubicin alone in patients with advanced hepatocellular carcinoma. Median durations of overall survival and progression-free survival were significantly longer in patients receiving sorafenib plus doxorubicin than in those receiving doxorubicin alone.[4] A prospective single-centre phase II study which included the patients with unresectable hepatocellular carcinoma (HCC)concluding that the combination of sorafenib and DEB-TACE in patients with unresectable HCC is well tolerated and safe, with most toxicities related to sorafenib.[15] This is the only indication for which sorafenib is listed on the PBS and hence the only Government-subsidised indication for sorafenib in Australia.[13] Along with renal cell carcinoma, hepatocellular carcinoma is one of the TGA-labelled indications for sorafenib.[10]

2.3 Thyroid cancer

A phase 3 clinical trial has started recruiting (November 2009) to use sorafenib for non-responsive thyroid cancer.[16] The results were presented at the ASCO 13th Annual Meeting and are the base for FDA approval. The Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The Phase 3 DECISION trial showed significant improvement in progression-free survival but not in overall survival. However, as is known, the side effects were very

frequent, specially hand and foot skin reaction.[17]

2.4 Desmoid tumors

A phase 3 clinical trial is under way testing the effectiveness of Sorafenib to treat desmoid tumors (also known as aggressive fibromatosis), after positive results in the first two trial stages. Dosage is typically half of that applied for malignant cancers (400 mg vs 800 mg). NCI are sponsoring this trial.[18][19]

3 Adverse effects

Adverse effects by frequency
Note: Potentially serious side effects are in ***bold****.*
Very common (>10% frequency)

- Lymphopenia
- **Hypophosphataemia**[Note 1]
- **Haemorrhage**[Note 2]
- Hypertension[Note 3]
- Diarrhea
- Rash
- Alopecia (hair loss; occurs in roughly 30% of patients receiving sorafenib)
- Hand-foot syndrome
- Pruritus (itchiness)
- Erythema
- Increased amylase
- Increased lipase
- Fatigue
- Pain[Note 4]
- Nausea
- Vomiting[Note 5][20]

Common (1-10% frequency)

- **Leucopoenia**[Note 6]
- **Neutropoenia**[Note 7]
- **Anaemia**[Note 8]
- **Thrombocytopenia**[Note 9]
- Anorexia (weight loss)
- **Hypocalcaemia**[Note 10]
- **Hypokalaemia**[Note 11]
- **Depression**
- Peripheral sensory neuropathy
- Tinnitus[Note 12]
- **Congestive heart failure**
- **Myocardial infarction**[Note 13]
- **Myocardial ischaemia**[Note 14]
- Hoarseness
- Constipation
- Stomatitis[Note 15]
- Dyspepsia[Note 16]
- Dysphagia[Note 17]
- Dry skin
- Exfoliative dermatitis
- Acne
- Skin desquamation
- Arthralgia[Note 18]
- Myalgia[Note 19]
- **Renal failure**[Note 20]
- Proteinuria[Note 21]
- Erectile dysfunction
- Asthenia (weakness)
- Fever
- Influenza-like illness
- Transient increase in transaminase

Uncommon (0.1-1% frequency)

- Folliculitis
- **Infection**
- Hypersensitivity reactions[Note 22]
- **Hypothyroidism**[Note 23]
- **Hyperthyroidism**[Note 24]
- **Hyponatraemia**[Note 25]

- **Dehydration**
- **Reversible posterior leukoencephalopathy**
- **Hypertensive crisis**
- Rhinorrhoea[Note 26]
- **Interstitial lung disease-like events**[Note 27]
- Gastro-oesophageal reflux disease (GORD)
- **Pancreatitis**[Note 28]
- **Gastritis**[Note 29]
- **Gastrointestinal perforations**[Note 30]
- Increase in bilirubin leading, potentially, to jaundice[Note 31]
- **Cholecystitis**[Note 32]
- **Cholangitis**[Note 33]
- Eczema
- **Erythema multiforme**[Note 34]
- **Keratoacanthoma**[Note 35]
- **Squamous cell carcinoma**
- Gynaecomastia (swelling of the breast tissue in men)
- **Transient increase in blood alkaline phosphatase**
- **INR abnormal**
- **Prothrombin level abnormal**
- **bulbous skin reaction**[21]

Rare (0.01-0.1% frequency)

- **QT interval prolongation**[Note 36]
- **Angiooedema**[Note 37]
- **Anaphylactic reaction**[Note 38]
- **Hepatitis**[Note 39]
- Radiation recall dermatitis
- **Stevens-Johnson syndrome**[Note 40]
- **Leucocytoclastic vasculitis**
- **Toxic epidermal necrolysis**[Note 41]
- **Nephrotic syndrome**
- **Rhabdomyolysis**[Note 42]

4 History

4.1 Renal cancer

Sorafenib was approved by the U.S. Food and Drug Administration (FDA) in December 2005,[22] and received European Commission marketing authorization in July 2006,[23] both for use in the treatment of advanced renal cancer.

4.2 Liver cancer

The European Commission granted marketing authorization to the drug for the treatment of patients with hepatocellular carcinoma(HCC), the most common form of liver cancer, in October 2007,[24] and FDA approval for this indication followed in November 2007.[25]

In November 2009, the UK's National Institute of Clinical Excellence declined to approve the drug for use within the NHS in England, Wales and Northern Ireland, stating that its effectiveness (increasing survival in primary liver cancer by 6 months) did not justify its high price, at up to £3000 per patient per month.[26] In Scotland the drug had already been refused authorization by the Scottish Medicines Consortium for use within NHS Scotland, for the same reason.[26]

In March 2012, the Indian Patent Office granted a domestic company, Natco Pharma, a license to manufacture generic Sorafenib, bringing its price down by 97%. Bayer sells a month's supply, 120 tablets, of Nexavar for₹280,000 (US$4,200). Natco Pharma will sell 120 tablets for ₹8,800 (US$130), while still paying a 6% royalty to Bayer. The royalty was later raised to 7% on appeal by Bayer.[27][28][29] Under Indian Patents Act, 2005 and the World Trade Organisation TRIPS Agreement, the government can issue a compulsory license when a drug is not available at an affordable price.[30]

4.3 Thyroid cancer

As of November 22, 2013, sorafenib has been approved by the FDA for the treatment of locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment.[31]

5 Research

5.1 Lung

In some kinds of lung cancer (with squamous-cell histology) sorafenib administered in addition to paclitaxel and carboplatin may be *detrimental* to patients.[32]

5.2 Brain (recurrent glioblastoma)

There is a phase I/II study at the Mayo Clinic[33] of sorafenib and CCI-779 (temsirolimus) for recurrent glioblastoma.

5.3 Desmoid tumor (aggressive fibromatosis)

A study performed in 2011 showed that Sorafenib is active against aggressive fibromatosis. This study is being used as justification for using Sorafenib as an initial course of treatment in some patients with aggressive fibromatosis.[34]

6 Nexavar controversy

In January 2014, Bayer's CEO stated that Nexavar was developed for "western patients who [could] afford it". At the prevailing prices, a kidney cancer patient would pay $96,000 (£58,000) for a year's course of the Bayer-made drug. However, the cost of the Indian version of the generic drug would be around $2,800 (£1,700).[35]

7 Notes

[1] Low blood phosphate levels

[2] Bleeding; including serious bleeds such as intracranial and intrapulmonary bleeds

[3] High blood pressure

[4] Including abdominal pain, headache, tumour pain, etc.

[5] Considered a low (~10-30%) risk chemotherapeutic agent for causing emesis)

[6] Low level of white blood cells in the blood

[7] Low level of neutrophils in the blood

[8] Low level of red blood cells in the blood

[9] Low level of plasma cells in the blood

[10] Low blood calcium

[11] Low blood potassium

[12] Hearing ringing in the ears

[13] Heart attack

[14] Lack of blood supply for the heart muscle

[15] Mouth swelling, also dry mouth and glossodynia

[16] Indigestion

[17] Not being able to swallow

[18] Sore joints

[19] Muscle aches

[20] Kidney failure

[21] Excreting protein [usually plasma proteins] in the urine. Not dangerous in itself but it is indicative kidney damage

[22] Including skin reactions and urticaria (hives)

[23] Underactive thyroid

[24] Overactive thyroid

[25] Low blood sodium

[26] Runny nose

[27] Pneumonitis, radiation pneumonitis, acute respiratory distress, etc.

[28] Swelling of the pancreas

[29] Swelling of the stomach

[30] Formation of a hole in the gastrointestinal tract, leading to potentially fatal bleeds

[31] Yellowing of the skin and eyes due to a failure of the liver to adequately cope with the amount of bilirubin produced by the day-to-day actions of the body

[32] Swelling of the gallbladder

[33] Swelling of the bile duct

[34] A potentially fatal skin reaction

[35] A fairly benign form of skin cancer

[36] A potentially fatal abnormality in the electrical activity of the heart

[37] Swelling of the skin and mucous membranes

[38] A potentially fatal allergic reaction

[39] Swelling of the liver

[40] A potentially fatal skin reaction

[41] A potentially fatal skin reaction

[42] The rapid breakdown of muscle tissue leading to the build-up of myoglobin in the blood and resulting in damage to the kidneys

8 References

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9 External links

- Nexavar.com – Manufacturer's website
- Prescribing Information – includes data from the key studies justifying the use of sorafenib for the treatment of kidney cancer (particularly clear cell renal cell carcinoma, which is associated with the von Hippel-Lindau gene)
- Patient Information from FDA
- Sorafenib in Treating Patients With Soft Tissue Sarcomas
- Sorafenib Sunitinib differences – diagram
- Clinical trial number *NCT00217399* at ClinicalTrials.gov – Sorafenib and Anastrozole in Treating Postmenopausal Women With Metastatic Breast Cancer
- Cipla launches Nexavar generic at 1/10 of Bayer's price

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