Drug Information Bulletin

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Content

Editorial

Death due to Tuberculosis is a global problem and this problem has been aggravated by development of Multidrug Resistant TB (MDR-TB) and Extremely Drug Resistant TB (XDR-TB). In 2014 about 480000 people developed MDR-TB globally and about 9.7% of these cases were XDR-TB.

The Govt. of India started a Revised National Tuberculosis Control Programme in 1997 to eradicate TB. RNTCP followed the WHO recommendation of Directly Observed Short Course (DOTS) strategy and reaches over a billion people in 632 districts. One of the shortfalls of this programme is discontinuation of treatment because of several reasons. Now Govt. of India recognizes services of private facilities, and are also taking help of NGOs to facilitate the RNTCP Programme.

Indian Pharmaceutical Association (IPA) is working for TB Care and Control utilizing the services of the community pharmacists as they are more accessible to the TB patient. In 2011 World Health Organization (WHO) signed a MOU with FIP at Hyderabad during FIP congress in 2011. Thereafter TBC, Govt. of India has signed a MOU with IPA, PCI, SEARPharm Forum & AIOCD for care & control of tuberculosis. As per this agreement IPA has started working in different states involving Pharmacists working in community Pharmacy and have experienced extremely positive outcome.

Recently RNTCP has given direction to all state TB officers to involve community pharmacists in this programme. Along with all other states, State TB officer of West Bengal has given direction to the Chief Municipal Health Officer and CMOH of all districts for involving community Pharmacist in RNTCP for early detection, referral of TB suspects for treatment, DOT provision for TB treatment and generating awareness about TB and MDR-TB. In a recent meeting IPA, BCDA and WHO consultant on TB has decided to support this programme in West Bengal.

This is a golden opportunity for the community pharmacists to serve the community and hope they will extend all sorts of help for success of this programme.

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New Drug: Enzalutamide

Approved indication: metastatic prostate cancer

40 mg capsules

Australian Medicines Handbook section 14.3.1

Prostate cancer is an androgen-dependent malignancy. Although medical or surgical castration reduces progression in the earlier stages, the cancer eventually becomes resistant and requires chemotherapy. The median survival time for men with castration-resistant disease is 1–2 years.

Androgen receptor signalling is increased at this late stage of the disease and is thought to be driven, in part, by over-expression of the androgen receptor. Anti-androgen treatments have therefore become a focus of research. Like abiraterone (Aust Prescr 2012;35:128-35), enzalutamide has been approved for patients with metastatic castration-resistant prostate cancer. Enzalutamide is an inhibitor of androgen receptor signalling and works by competitively blocking the binding of androgen to its receptor.

The efficacy and safety of enzalutamide has been assessed in a phase III trial.[1] Men who had already been treated with docetaxel were randomised to enzalutamide 160 mg once daily (800 patients) or placebo (399 patients). Corticosteroids were allowed during the study and patients continued androgen deprivation therapy.

Enzalutamide treatment was continued until the disease progressed. The median duration of treatment was 8.3 months in the enzalutamide group versus 3 months in the placebo group. Median overall survival was significantly longer for enzalutamide than with placebo (18.4 vs 13.6 months, $p<0.001$). Because of the observed benefit, the study was stopped at the prespecified interim analysis and patients in the placebo group were offered enzalutamide.

The most common adverse events with enzalutamide were asthenia or fatigue (50.6% of people), back pain (26.4%), arthralgia (20.5%), hot flushes (20.3%), peripheral oedema (15.4%), musculoskeletal pain (15%) and headache (12.1%). These were more frequent with enzalutamide than with placebo. Neutropenia was also more common with enzalutamide than with placebo (15% vs 6%), and 1% of men in the enzalutamide group died from an infection compared to 0.3% in the placebo group. Falls or injuries from falls (4.6% vs 1.3%) and hallucinations (1.6% vs 0.3%) were also more frequently reported with enzalutamide.

Enzalutamide comes with a warning about seizures. In the trial, 7 of 800 men given enzalutamide had a seizure, compared to no seizures with placebo.[1] Caution is urged in patients with a history of seizures, brain injury, stroke, tumours in the brain, alcoholism or concomitant use of medicines that reduce the seizure threshold.

Cardiac disorders were reported in 6% of those taking enzalutamide[1] even though men with recent cardiovascular disease were excluded from the trial (recent myocardial infarction or unstable angina, a long QT interval, bradycardia or uncontrolled hypertension). Hypertension (6.6%) has also been reported with enzalutamide.

Following oral administration of enzalutamide, maximum plasma concentrations are observed within 1–2 hours. Oral bioavailability is high (≥84.2%). The mean terminal half-life is approximately six days and steady state is reached after a month. Most of the dose is excreted in the urine (71%), with a minor portion excreted in the faeces (13.6%).

Caution is urged when prescribing enzalutamide to people with moderate hepatic impairment and it is not recommended in those with severe impairment. Care should also be taken in

those with severe renal impairment or end-stage renal disease.

Enzalutamide is extensively metabolised, mainly by cytochrome P450 (CYP) 2C8, so strong inhibitors (gemfibrozil) or inducers (rifampicin) of this enzyme should be avoided if possible. If a CYP2C8 inhibitor is co-prescribed, the enzalutamide dose should be halved. Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19 so there is potential for drug interactions with substrates of these enzymes such as midazolam, warfarin and omeprazole. Enzalutamide may also affect P-glycoprotein so substrates of this transporter with a narrow therapeutic range (e.g. colchicine, dabigatran, digoxin) may require dose adjustment. There may be an increased risk of liver injury with paracetamol in patients being treated with enzyme inducers.

Enzalutamide provides another option for men with metastatic castration-resistant prostate cancer. Although it prolongs survival by a median of 4.8 months, enzalutamide carries a risk of seizures as well as numerous drug interactions. It is not known how it will compare to abiraterone. Enzalutamide is also being investigated in the treatment of metastatic prostate cancer before chemotherapy.[2]

References

1. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. AFFIRM Investigators . Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187-97.[PubMed]
2. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. PREVAIL Investigators . Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med2014;371:424-33. [PMC free article] [PubMed]

Ref. Australian Prescriber

Indian situation: Enzalutamide 40 mg soft Capsule has been approved by CDSCO on 18.12.2015 "For the treatment of adults with metastatic castration resistant prostate cancer whose disease has progessed on or after Docetaxel therapy".

Afatinib maleate: Risk of acute pancreatitis

The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for afatinib maleate (Giotrif®) has been updated to include the risk of acute pancreatitis as a clinically significant adverse reaction.

Afatinib is used to treat unresectable or recurrent epidermal growth factor receptor (EGFR) mutation-positive non-small-cell-lung cancer.

A total of four cases of acute pancreatitis have been reported with the use of afatinib in Japan. Of these, a causal relationship could not be excluded in two cases. Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Precautions to the package insert have been revised to include:

Acute pancreatitis: Acute pancreatitis may occur. Patients should be carefully monitored. If abnormalities, such as abdominal pain and increased serum amylase are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

Reference: Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Chlorhexidine antiseptic non-prescription topical products:Serious allergic reactions

Health Canada has conducted a safety review which shows that topical

chlorhexidine may cause serious allergic anaphylactic reactions when used in the mouth, on open wounds, orimmediately before or during surgery.

Chlorhexidine topical products are available without a prescription at concentrations of 2-4% in various formulations such as creams, liquids, gels and sprays. They are used as a topical antiseptic to reduce the risk of bacterial infection.

Symptoms of a serious allergic reaction, including anaphylaxis, may include itchy hives with swelling of the face, eyes, lips, mouth or throat; difficulty breathing; throat tightness or hoarseness; and fainting. An anaphylactic reaction is a serious and potentially life-threatening hypersensitivity reaction.

The review was triggered by published cases of serious allergic reactions linked to the use of topical chlorhexidine. At the time of the review, Health Canada had received 53 reports of serious allergic reactions with use of non-prescription topical chlorhexidine products, of which three were anaphylactic reactions.

Health Canada's Antiseptic Skin Cleansers monograph already requires that the labelling for non-prescription topical chlorhexidine products include a warning statement to minimize the risk of allergic reactions. Health Canada will work to update the product information with these new findings.

Reference: Summary Safety Review, Health Canada, 13 May 2016 (*www.hc-sc.gc.ca*)

Canagliflozin:Risk of leg and foot amputations- under investigation

The US FDA has issued a safety alert informing the public of investigations into the potential risk in leg and foot amputations with use of canagliflozin (Invokana® and Invokamet®).

Canagliflozin is used in combination with diet and exercise to lower blood sugar in adults with type 2 diabetes. It is available in an individual preparation and as a combination with metformin.

An increased risk of leg and foot amputations was identified in the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial.

This risk has not been observed in a second similar trial, the CANVAS-R. Health-care professionals are advised to follow recommendations in the canagliflozin drug labels, and to monitor patients for signs and symptoms such as any new pain or tenderness, sores or ulcers, or infections in their legs or feet.

The FDA continues to evaluate this safety issue and will update the public when more information is obtained.

Reference: Drug Safety Communication, US FDA, 18 May 2016 (*www.fda.gov*)

Fluconazole: Risk of miscarriage in pregnancy- under investigation

The US FDA is investigating results from a Danish study which suggests that there is an increased risk of miscarriage with the use of oral fluconazole (Diflucan®) during pregnancy.

Oral fluconazole is used to treat yeast infections of the vaginal area, mouth and oesophagus.

It is also used to treat C*ryptococcal* meningitis and is often used prophylactically in immunocompromised patients.

The FDA advises cautious prescribing of oral fluconazole in pregnancy, until the FDA reviews this study and other available data.

Reference: Drug Safety Communication, US FDA, 26 April 2016 (*www.fda.gov*)

Life expectancy grows for chronic myeloid leukemia patients

An analysis of data from a patient registry in Sweden found that people who are treated for chronic myeloid leukemia have a life expectancy that is nearing that of the general population. Treatments such as imatinib mesylate and other tyrosine kinase inhibitors and allogeneic stem cell transplantation are contributing to

increases in survival, according to the study.

Reference: MedPage Today

FDA, biotechnology industry reach consensus on biosimilar user fees

Biotechnology industry representatives and the FDA settled on a draft commitment letter representing agreements on the second iteration of the Biosimilar User Fee Act, a five-year funding agreement between the FDA and stakeholders to support the agency's review program for biosimilar drugs. Industry groups that participated in the negotiations include BIO, the Generic Pharmaceutical Association, the Pharmaceutical Research and Manufacturers of America and the Biosimilars Forum.

References: Regulatory Focus

The brochure of 68th IPC was released by Sri N. Chandrababu Naidu, Chief Minister of Andhra Pradesh

Announcement: IPC