Drug Information Bulletin

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Volume: 09 ***Number: 17*** ***22nd November 2015***

Content

Editorial

This year 54th National Pharmacy Week (NPW) is being celebrated with the theme of "Responsible Use of Antibiotics Saves Lives" by Indian Pharmaceutical Association**.** Incidentally WHO is also celebrating 16-22nd November as "Antibiotic Awareness Week". Antimicrobial resistance is a serious global problem. Most antimicrobials are now resistant to a large number of microbes, developing several problems like- MDR & XDR strains of Tuberculosis. Very few antimicrobials have been developed during the last decade and pharmaceutical industries are reluctant to invest in R & D of antimicrobials, as the return is low due to its short life cycle. Major reasons for developing antimicrobial resistance are-

1. Inappropriate prescribing e. g: prescribing third generation antibiotics where first generation drugs would suffice
2. Inappropriate use like non adherence to the antimicrobial regimen
3. Self prescribing
4. Resistant strains of bacteria & virus being transmitted via Nosocomial infections
5. Indiscriminate use of Antimicrobials in live stocks (Dairies, Piggeries, Hatcheries, Fisheries etc.)

The situation is more complicated in developing countries as all of the antibiotics are available from community pharmacy without prescription and proper counseling is not provided due to absence of pharmacists in the community pharmacies. Moreover aggressive marketing by pharmaceutical companies sometimes facilitates inappropriate use of costlier antibiotics, where it is quite unnecessary.

A two pronged strategy may help combating this issue- firstly a well formulated Antibiotic Policy of a country and the other is generating meaningful awareness among health care providers as well as the general public.

Pharmacists have knowledge of antibiotics and their proper application, and clinically this can help doctors for proper selection of an appropriate and viable treatment regime. Pharmacists are the major interface between physicians and patients, and hence can counsel patients better regarding importance of completing an antimicrobial regimen, as well as dissuade the patients from self prescribing antibiotics, which leads to breeding antimicrobial resistance and cross resistance. Considering this situation IPA, Bengal Branch has decided to start a project on combating antimicrobial resistance under an ongoing program titled "KYM" – Know your Medicines. They are also organizing a one day National Workshop on "Combating Antimicrobial Resistance" on 22nd November 2015.

Hope such several programme will be taken throughout the country during the NPW and will continue the same in future to avoid the further emergence and spread of antimicrobial resistance.

Dr. Subhash C. Mandal,
Editor

New Drug: Idelalisib

Approved indication: chronic lymphocytic leukaemia, follicular lymphoma
100 mg and 150 mg tablets

Like ibrutinib,1 idelalisib is an oral anticancer drug that targets B-cell cancers. It works by inhibiting phosphatidylinositol 3-kinase. This enzyme is overactive in B-cell cancers and is involved in driving proliferation, migration and survival of malignant cells.
Idelalisib is registered for two indications:

- in combination with rituximab for chronic lymphocytic leukaemia and small lymphocytic lymphoma when chemotherapy is not suitable, in people who have relapsed after treatment or have the chromosome 17p deletion or TP53 mutation
- monotherapy for refractory follicular lymphoma.

Chronic lymphocytic leukaemia
The approval of idelalisib for relapsed chronic lymphocytic leukaemia is based on a pivotal phase III trial of 220 patients.2The median age of randomised patients was 71 years. Two-thirds of them had advanced disease and the median time since initial diagnosis was nine years. Patients were heavily pre-treated (regimens included rituximab, cyclophosphamide, fludarabine and bendamustine) and were considered too unwell for chemotherapy.
In total, 80% of the patients lacked somatic hypermutation of the gene encoding the immunoglobulin heavy-chain variable region, and 40% carried the 17p deletion or TP53 mutation. These genetic characteristics are generally associated with poorer outcomes.
Patients received intravenous rituximab with either oral idelalisib or placebo. After 24 weeks, the rate of progression-free survival was significantly higher with idelalisib than with placebo ($p<0.001$,. The overall response rate, assessed using serial CT or MRI of the neck, chest, abdomen and pelvis, was significantly higher in the idelalisib group compared to the placebo group (81% vs 13%, $p<0.001$). These were all partial responses.2
Idelalisib was also better than placebo in subgroup analyses of patients with unmutated immunoglobulin heavy-chain variable region, or the 17p deletion or TP53 mutation. The trial was terminated at the interim analysis because of the superior efficacy of idelalisib combined with rituximab.
Single-arm trials of idelalisib combined with chemotherapy or immunotherapy generally found similar overall response rates (72% or above). However at the time of writing, these trials do not appear to have been published in full.
Follicular lymphoma
The approval of idelalisib as a monotherapy for refractory follicular lymphoma was based on a pivotal phase II uncontrolled trial of 125 patients with relapsed indolent lymphoma.3 Of the participants, 72 had follicular lymphoma, 28 had small lymphocytic lymphoma, 15 had marginal-zone lymphoma and 10 had lymphoblastic lymphoma. Patients had received a median of four previous regimens and most of them were refractory to rituximab and an alkylating agent such as cyclophosphamide. Their median age was 64 years.
The median duration of treatment was 6.6 months. More than half of patients responded to treatment – these were mainly partial responses. Rates of response seemed to be comparable across the different disease subtypes.
Adverse effects and precautions: The most common adverse reactions (any grade) to idelalisib include neutropenia (50%), increased transaminases (50%), diarrhoea (38%), fever (32%), rash (24%) and pneumonitis (3%). These events can be serious (grade 3) in some cases and increased monitoring, dose interruption or treatment discontinuation may be needed.
In the indolent lymphoma trial there were 28 deaths. Most were related to disease

progression (20 deaths). Other causes included pneumonia (3 patients), cardiac arrest, cardiac failure, splenic infarction, septic shock and pneumonitis (1 patient each).3

As elevated liver enzymes are so common, it is important to monitor alanine transaminase, aspartate transaminase and bilirubin fortnightly, at least for the first three months of treatment. Reactivation of hepatitis has occurred with idelalisib and all patients should be screened for hepatitis B and C before they start treatment. Close monitoring for toxicity is recommended if idelalisib is initiated in patients with severe hepatic impairment.

Severe diarrhoea or colitis occurred in 14% of patients across the trials. If diarrhoea occurs, make sure the patient is adequately hydrated, particularly those with pre-existing renal failure. Infections such as *Clostridium difficile* should be excluded. Intestinal perforation has been reported with idelalisib. This was fatal in some cases. Treatment should be stopped if perforation occurs.

Although live vaccines are not recommended during idelalisib treatment, they can be given to high-risk patients before treatment is started.

Pharmacokinetics: The recommended dose of idelalisib is 150 mg orally twice a day. Peak plasma concentrations are reached within 2–4 hours after oral administration. Idelalisib is mainly metabolised by aldehyde oxidase, but also by cytochrome P450 (CYP) 3A and UGT1A4. The elimination half-life is around eight hours and metabolites are excreted in the faeces (78%) and urine (15%).

Drug interactions: Concomitant strong CYP3A inducers (e.g. rifampicin, phenytoin, carbamazepine, St John's wort) may reduce plasma concentrations of idelalisib and should be avoided. Strong inhibitors may elevate idelalisib concentrations so increased monitoring for toxicity is recommended.

Caution is urged if idelalisib is given to patients taking CYP3A substrates with a narrow therapeutic index (e.g. cisapride, fentanyl). Idelalisib is a strong inhibitor of CYP3A and may increase exposure to substrates such as warfarin, some antiarrhythmic drugs, calcium channel blockers and statins.

Conclusions: Idelalisib seems to benefit pre-treated, older patients with chronic lymphocytic leukaemia and follicular lymphoma. However, adverse effects are common and often limit treatment. In chronic lymphocytic leukaemia, the long-term safety and effectiveness of idelalisib remains to be determined.

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3. Gopal AK, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-18.http://dx.doi.org/10.1056/NEJMoa1314583

Ref. Australian Prescriber

Roche to close 4 plants in shift to specialized drugs

Roche plans to close manufacturing facilities in Ireland, Spain, Italy and the US as part of a shift from its small-molecule portfolio toward more specialized drugs produced in lower volumes. The company also plans to invest nearly $300 million in its facility in Kaiseraugst, Switzerland, to manufacture the new generation of specialized drugs.

Ref. Pharma Times

Physician group calls for ban on DTC drug, device ads

The American Medical Association said direct-to-consumer prescription drug and medical device ads should be banned because they increase the demand for

expensive new treatments and drive increases in drug prices. A pharmaceutical industry group said the advertising raises consumer awareness of available treatments.
Ref. Reuters

West Bengal IPA starts KYM to combat microbial resistance, to emphasize pharmacists' role in patient counselling

Giving emphasis to newly introduced Pharmacy Practice Regulations (PPR) 2015 for reinforcing the role of registered pharmacists in counseling patients on the use of antibiotics and dissuade them from self prescribing, the West Bengal branch of the Indian Pharmaceutical Association has started a project on combating antimicrobial resistance under a programme titled, 'Know Your Medicines' or KYM.

The project is giving priority to the role of pharmacists in dispensing drugs as well as counseling patients on the use of drugs.

Briefing Pharmabiz about the project, the president of WB IPA, Dr. C Subash Mandal said antimicrobial resistance is a serious global problem today. Most anti microbials are now resistant to a large number of microbes, developing several problems like MRSA, MDR and XDR strains of tuberculosis. There are several reasons for developing antimicrobial resistance like inappropriate prescribing.

Other reasons may include inappropriate use like non adherence to the antimicrobial regimen, self medication, resistant strains of bacteria and virus being transmitted through nosocomial infection or hospital-acquired infection, and indiscriminate use of antimicrobials in live stocks such as dairies, piggeries, hatcheries, fisheries etc.

According to him, the situation is more complicated in developing countries as all of the antibiotics available from community pharmacies are without prescription and proper counseling on its use is not provided to the patients due to several reasons. That is where the importance of new Pharmacy Practice Regulations emerges and the role of qualified pharmacists rises. The KYM programme is aimed to address all the complications arising out of the use of antibiotics.

He said the PPR 2015 will be effective in combating this problem. Moreover aggressive marketing by pharmaceutical companies sometimes facilitates inappropriate use of costlier antibiotics, where it is quite unnecessary. Pharmacists have knowledge of antibiotics and their proper application, and clinically this can help doctors for proper selection of an appropriate and viable treatment regime. Pharmacists are the major interface between physicians and patients.

A two pronged strategy may help combating this issue, first there should be a well formulated antibiotic policy, and secondly, programmes should be introduced to generate meaningful awareness among health care providers as well as the general public.

Dr. Mandal, who is working as a drugs control officer in West Bengal, said very few antimicrobials have been developed during the last decade, but the pharmaceutical industries are reluctant to invest in R&D of antimicrobials because the return from the investment is low due to its short life cycle.

In West Bengal, the unit of IPA has introduced several programmes in electronic and social media to discourage the irrational and unnecessary use of antibiotics. Informative leaflets are being distributed in all the retail pharmacy shops in collaboration with Bengal Chemists & Druggists Association.

Kolkata district has been selected as model district towards increasing public awareness. Kiosks have been set up at prominent places of big hospitals and informative posters have been displayed there. Counseling of patients is also done in various hospitals by the pharmacists. Besides, seminars on 'responsible use of antibiotics' have been conducted in different districts as part of this year's National Pharmacy Week celebration.
Ref. Pharmabiz