Original Article

Striking balance between expedited review and expecting efficacious anticancer drug and biologics: An ongoing challenge

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Abstract

Objective: The objective of this study is to assess the postmarketing status: Efficacy and safety drugs and biologics related with cancer approved under expedited review.

Methods: This observational, analytical study was carried between January and April 2016 by the Department of Pharmacology and Medical Oncology, Saveetha Medical College. Drugs approved under expedited review, fast-track status and its association with anti-cancer effects, postmarketing efficacy and safety, propensity to induce the second tumor was noted. Drug approval status and average time of review process were obtained from the United States-Food and Drug Administration (FDA), Center for Drugs and Biologics Center (Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research). Postmarketing adverse events and safety issues were collected FDA adverse effects reporting system. Further, evidence efficacy and safety of drugs were taken from various meta-analysis, reports on BioMed journals, and Cochrane systematic reviews.

Results: In the last 5 years, 166 products were approved by expedited review. Out of 166, 48 (28.9%) drugs/biologics are anticancer drugs and drugs used in precancerous conditions. The average time of review varies from19 months to 8.2 months. Out of these 48 molecules, 37 (77%) molecules received serious adverse event alert. Positive correlation is seen between average time of review and number of adverse events reported. Seven (14.5%) drugs were proven to induce second tumor among receivers.

Conclusion: Although expedited review facilitates faster approval of drugs; selection and assessment criteria should be stringent to prevent clinical failure, serious adverse effects of such drugs exposed to many individuals. Focus should be given developing chemosensitizing molecule and evaluation of metronomic regimen which is being more optimistic in current cancer therapeutics.

Keywords: Expedited drug review, fast-track approval, metronomic therapy, priority review

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INTRODUCTION

Cancer-related morbidity and mortality are increasing steadily as a part of global epidemiologic transition. In the last year, nearly 14 million cases of cancer were detected and mortality though reduced still remains a major unmet need in medical scenario. In South Asia, about 5 lakhs cancer patients are

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dying every year in the Indian subcontinent alone and overall mortality of cancer patients in South Asia approaches is escalating every year due to low socioeconomic status and poor access to good cost-effective medicines.[1] Every step has been taken from medical fraternity; they are cancer awareness, prevention, and inventing efficacious anticancer drugs and good palliative care approach. We are in transition between conventional chemotherapy to targeted therapy that is expected to give us higher number of cancer cure and even good quality of life. Availability of such new efficacious drugs depends on its discovery and rapidity of available to global population after careful interpretation.

The United States-Food and Drug Administration (US-FDA) has taken several measures to reduce the time of evaluating to expedite review process of drug that fills an unmet medical need. The expedited review processes are fast-track approval process, in which a new chemical moiety (drug) can be approved based on its efficacy proven from single phase 2 trial and review process usually completed within 180 working days. This is shouldered by priority review program and accelerated drug approval program; all the expedited drug review procedure enables the investigator and sponsor to contact and to seek guidance from regulatory authorities to review the molecules and grant approval with the objective of making it available for the needy within a shorter span of drug development.[2,3]

There are critics and few evidence-based consensus states that the drugs approved by expedited review are not having expected clinical achievement and also number of serious adverse effects is more. Striking balance between reviewing safety and efficacy and approving for marketing is an ongoing challenge, especially in case of anticancer drugs and biologics. Hence, this was undertaken to analyze recent scenario about number of anticancer drugs reviewed under expedited manner.[4]

METHODS

This observational, analytical study was carried out between January and June 2016 by the Department of Pharmacology and Department of Medical Oncology in our tertiary care teaching center. Anti-cancer drugs and biologics approved from 2011 to 2015 were collected from official website US-FDA, Center for Drugs and Biologics, new drug approvals (Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research). Anticancer drugs and biologics related to cancer, proposed indication, average time of review, number of phases of clinical trials evaluated before approval were obtained from the food and administration annual statement of novel drug release between 2011 and 2015.

Drugs approved under expedited review, fast-track status and its association with anticancer effects, postmarketing efficacy and safety, propensity to induce second tumor were noted. Postmarketing adverse events and safety issues were collected FDA adverse effects reporting system. Further, evidence efficacy and safety of drugs were taken from various meta-analyses, report on credible Biomed journals and systematic reviews.

RESULTS

Data were entered in MS Excel, descriptive statistics, and nonparametric test was used to describe the proportion and significance of association using Statistical Package of Social Sciences software version 17 (SSPS IBM Inc 17, USA). In the last 5 years, 166 products were approved by expedited review. Out of 166, 48 (28.9%) drugs/biologics were anticancer drugs and drugs used in precancerous conditions. The average time of review varies from 19 months to 8.2 months. Out of these 48 molecules, 37 (77%) molecules received serious adverse event (SAE) alert. Positive correlation was seen between average time of review and number of adverse events reported. Seven (14.5%) drugs were proven to induce the second tumor among receivers. Twenty-two (45.7%) molecules were proven to do well in real cancer treatment scenario. Statistical significance between numbers of molecules showing efficacy in trial versus in clinical scenario ($P < 0.05$) and similar correlation was seen with lesser the time of evaluation and more of adverse events reported.

Number of molecule approved and time of evaluation is depicted in Table 1. SAEs that resulted in withdrawn or drug labeling change are shown in Table 2. Molecules proven to be beneficial are given in Table 3.

DISCUSSION

Briefing of objective

Our study objective was focused to analyze the expected efficacy of drugs those were given accelerated approval between that is approved by expedited review process and their current status. Overall analysis shows expedited drug review may undermine the safety involved while evaluating the risk. This was explained in some other critical analysis as well.[5] Even some of drugs other than approved for cancer, such as selective cyclooxygenase inhibitors approved by fast-track review process

Table 1: Number of anticancer drugs and biologics approved and their average time of evaluation

Year	Number of molecules	Average time of evaluation (months)
2011	8	11.2
2012	9	9
2013	9	8.7
2014	13	8.2
2015	11	6.4

Table 2: Some of the recently approved expedited anticancer drugs and biologics and their associated significant adverse effects (risk outweighs the benefits)

Drug/biologics	Indication	Premarketing status	Postmarketing status
Ponatinib	Chronic myeloid leukemia	Adverse effect was not detected within the preanalysis review	Withdrawn due to its propensity to cause fatal veno-occulsive disease
Ado trastuzumab	Breast cancer	Granted approval against safety involved	Cardiotoxicity, pancreatitis, neonatal pulmonary hypoplasia
Crizotinib	Lung cancer	Adverse effect was not detected within the preanalysis review	Visual field defect, pneumonitis
Sofosbuvir, simeprevir	Hepatitis C-related	Adverse effect was not detected	Cardiac arrhythmia
Dasabuvir, telaprevir	complications	Adverse effect was not detected within	Hepatic failure, hypersensitivity
Ombitasvir, paritaprevir	including hepatocellular cancer	the preanalysis review	
Ipilimumab	Late stage melanoma	Adverse effect was not detected	Fatal allergic reaction
Vemurafenib	Late stage melanoma	Granted approval against safety involved	Cutaneous squamous cell cancer cancer
Ofatumumab	Anti CD 20	Adverse effect was not detected within the preanalysis review	Hepatitis B reactivation
Adalimumab	Anti CD 52	Adverse effect was not detected within the preanalysis review	Hepatosplenic lymphoma Optic neuritis Drug-induced sarcoidosis
Brentuximab vedotin	Anti CD 30	Adverse effect was not detected within the preanalysis review	Progressive multifocal leukoencephalopathy
Cetuximab	Colon cancer	Adverse effect was not detected within the preanalysis review	Hepatosplenic lymphoma
Pomalidomide	Multiple myeloma	Granted approval against safety involved	Hepatotoxicity

Table 3: Some of the recently approved expedited anticancer drugs and biologics with goog clinical success rate (benefits outweighs the risk)

Drug/biologics	Indication
Abiraterone	Prostate cancer
Vandetanib	Thyroid cancer
Eribulin	Breast cancer
vismodegib	Basal cell carcinoma
Enzalutamide	Prostate cancer
Ruxolitinib	Myelofibrosis
Glucarpidase	Methotrexate clevaging enzyme
Asparaginase	Acute leukemias
Bosutinib	Chronic myeloid leukemia

were subsequently withdrawn due to increased cardiovascular events. Hence, refining the review process will yield number efficacious anticancer drug and biologics as discussed below.

Critical findings

In our analysis of expedited drugs in the last quintile, review program recently provided molecules that are clinical successful and clinically insignificant molecules as well. Some of those molecules are being used add-on therapy (abiraterone for resistant metastatic prostate cancer) or as an adjuvant therapy (eribulin for advanced breast cancer) or used to reduce toxicity of anticancer drugs (glucarpidase for methotrexate toxicity). Even, some of the drugs were first of its kind including ruxolitinib which was the first approved for myelofibrosis.[5-9]

To curtail the clinical failure of expedited drug review process, number of molecules taken for expedited review should be curtailed and criteria framed for fast-track designation must be followed strictly. Ponatinib was a classical example which was approved for chronic myeloid leukemia based on single phase 2 trial with historical control. The justification for such accelerated approval when imatinib and dasatinib, nilotinib for imatinib resistance cases are still in place is questionable. FDA did not provide what was the unmet need found here. Almost all the anti-hepatitis C drugs approved on viral load reduction as a surrogate end-point is associated with very significant adverse effects. To note the latest, ombitasvir, and paritaprevir were approved on July 2015, and severe fatal hepatic injury was reported within 4 weeks of treatment on black box warning issued by FDA October 2015, which raises the question of its safety evaluation was predicted or unpredicted during the review process within 6 months. Question of efficacy versus safety may favor the drug; question of efficacy versus ethics is not same. Classically, vemurafenib which increases lifespan of late stage melanoma merely 3–4 months has high propensity to cause cutaneous cancers among survivors. Biologics and immunomodulators are seems to be not right candidates for short review process. These molecules are complex and interact with many biological signaling proteins while curing an autoimmune disease or cancer, they also induce another cancer, which are highly fatal-like hepatosplenic lymphoma.[10-15]

Suggestions from our study

To produce an efficacious anticancer drug or biologics, regulatory authorities should evaluate the molecule adequately. While ascertaining efficacy, surrogate end-points must be crossmatched with expected clinical success rate based on precursor molecule, if available and nature of aggressiveness of tumor and its natural life expectancy. Unnecessary accelerated approval may not fetch optimal benefits while purging cost and time of developing molecule. Outcome parameters to

improve patient quality of life must be also considered along with other outcome parameters such as disease-free progression and survival rate.[16,17]

CONCLUSION

Expedited drug review have given us wonderful molecules including cisplatin, paclitaxel, and so-called "magic bullet" imagine; however, recent trend shown to be trivial in assessment based on outcome of molecule after its approval.

At present, when most of cancer has fixed regimen and prognosis for each stage of various cancers is known, drug development should focus on developing chemosensitizing molecules to break anticancer drug resistance and adopting methods such as metronomic chemotherapy which will considerable reduce number of molecules taken for expedited review and indirectly will provide more substantial time and evaluation of molecule.[18-20]

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Conflicts of interest
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