मानवाची उत्पत्ती व विकासाचे विविध टप्पे

Human Origin and Different Steps in Its Development

संपादक
प्रा. डॉ. एन.बी. सुर्यवंशी

स्वा.रा.ती.म.विद्यापीठ, नांदेड व शिवनेरी महाविद्यालय, शिरुर अनंतपाळ
(महाराष्ट्र) यांच्या संयुक्त विद्यमाने आंतरविद्याशाखीय राष्ट्रीय परिषद
२७ फेब्रुवारी २०१६

मानवाची उत्पत्ती व विकासाचे विविध टप्पे

संपादक

प्रा. डॉ. एन.बी. सुर्यवंशी

संपादक मंडळ

प्रा. शिंदे पी.आर.
प्रा. रोडगे जी.एस.
प्रा. चव्हाण एस. आर.
प्रा. डॉ. वागलगावे एच.डी.
प्रा. इंगळे ए.आर.
प्रा. डॉ. माने एस.व्ही.
प्रा. जाधव डी.बी.
प्रा.डॉ. धुमाळे डी.के.
प्रा. वडनेरे एस.एम.
प्रा. डॉ. सोमवंशी एम. वाय.
प्रा. डॉ. लाटे ए. एम.
प्रा. कुरे के.व्ही.
प्रा. गायकवाड एम.जी.
प्रा. हालसे बी.पी.
प्रा. जाधव ओ. डब्ल्यु
प्रा. बोंडगे ए.एस.
प्रा. कांबळे एस.एन.
डॉ. जाधव आर.आर.

मार्गदर्शक

प्राचार्य डॉ. बी. जी. सोनवणे

अरुणा प्रकाशन, लातूर

ISBN 978-93-5240-040-9

83.
Effect of Anticancer drugs on human body

Anil B. Chidrawar
Department of Chemistry, Degloor College,
Degloor, S.R.T.M.U. Nanded- 431717
Email : anilchidrawar74@gmail.com

Abstract :

The discovery and development of anticancer drugs, especially cytotoxic agents, differ significantly from the drug development process for any other indication. The unique challenges and opportunities in working with these agents are reflected in each stage of the drug development process. This research will highlight the unique aspects of anticancer drug discovery and development.

Key words : Anticancer drugs, *chemotherapy*, **lymphoid tissue, spermatogenic cells,** antineoplastic drug.

Introduction : Anticancer drug, also called antineoplastic drug, any drug that is effective in the treatment of malignant, or cancerous, disease. There are several major classes of anticancer drugs; these include alkylating agents, antimetabolites, natural products, and hormones. In addition, there are a number of drugs that do not fall within those classes but that demonstrate anticancer activity and thus are used in the treatment of malignant disease. The term *chemotherapy* frequently is equated with the use of anticancer drugs, although it more accurately refers to the use of chemical compounds to treat disease generally. Next to heart diseases, cancer is the major killer of mankind. Irrespective of the etiology, cancer is basically a disease of cells characterized by loss of normal cellular growth, maturation and multiplication and thus homeostasis is disturbed. **The treatment of cancer with drugs was started by Huggins and Hoges in 1941, with the discovery that oestrogens palliate prostate cancer. Subsequently the polyfunctional alkylating agents were developed during World War II. Since**

then a number of chemotherapeutic agents have become available for the treatment of cancer. One of the first drugs that was used clinically in modern medicine for the treatment of cancer was the alkylating agent mechlorethamine, a nitrogen mustard that in the 1940s was found to be effective in treating lymphomas. In 1956 the antimetabolite methotrexate became the first drug to cure a solid tumour, and the following year 5-fluorouracil was introduced as the first of a new class of tumour-fighting compounds known as pyrimidine analogs. Since then many anticancer drugs have been developed and used with much success. The decision to use a certain anticancer drug depends on many factors, including the type and location of the cancer, its severity, whether surgery or radiation therapy can or should be used, and the side effects associated with the drug. Most anticancer drugs are administered intravenously; however, some can be taken orally, and others can be injected intramuscularly or intrathecally (within the spinal cord).

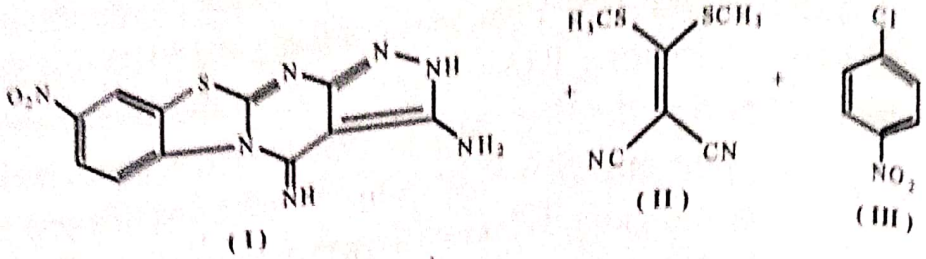
Experimental Section : All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ^{1}H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by Thin layer chromatography.

Materials and Methods :

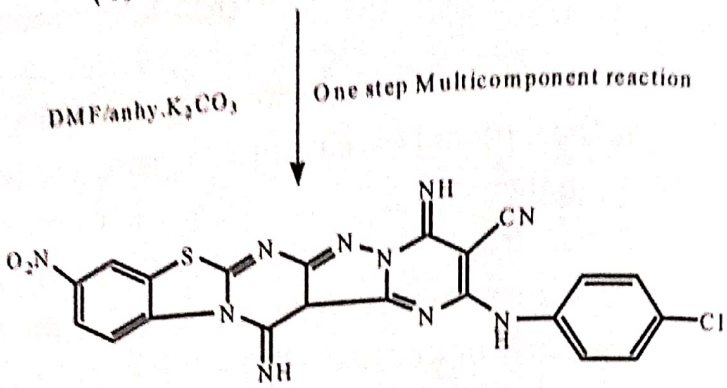
Synthesis of 3-cyano-4,14-diimino-2-(p-chloroanilino)-10-nitro pyrimido [2,3-*b*] pyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3]benzothiazole.

A mixture of 3-amino-4-imino-8-nitro-2H-pyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole (I) [1mole], bis-methylthio methylene malononitrile (II) [1mole] and p-chloroaniline (III) was refluxed in the presence of of dimethyl formamide (5ml) and a pinch of anhydrous potassium carbonate for six hours gives 3-cyano-4,14-diimino-2-(p-chloroanilino)-10-nitro pyrimido [2,3-*b*] pyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole (IV). The progress of reaction was monitored on TLC. After completion of reaction, the reaction mixture was cooled to room temperature and poured on ice cold water. The separated solid

ISBN 978-93-5240-040-9
product was filtered, washed with water and recrystallized from ethanol to give respective products.



(I) (II) (III)



(IV)

Principles of Chemotherapy : Many forms of chemotherapy are targeted at the process of cell division. The rationale being that cancer cells are more likely to be replicating than normal cells. Unfortunately as their action is not specific, they are associated with significant toxicity. An understanding of the principles of tumour biology and cellular kinetics is helpful to appreciate the mechanisms of action of cancer chemotherapy.

Drug Development : Conventional screening models for anticancer agents are geared toward the selection of cytotoxic drugs. The animal screening models predominantly focus 50 A.S. Narang and D.S. Desai on tumor regression and survival advantage, while the early stage human clinical trials are aimed at determining the limiting dose where high drug related toxicity is observed. Toxicity and tumor-regression effects of cytotoxic agents are based on the same mechanism. Thus, these agents are dosed to the allowable maximum levels where serious toxicity is not observed. The molecularly targeted agents, on the other hand, act by mechanisms that may not result in direct and significant toxicity. These agents act on the extra cellular, trans membrane, or nonnuclear

ISBN 978-93-5240-040-9

intracellular processes and are exemplified by receptor tyrosine kinase inhibitors, farnesyltransferase inhibitors, matrix metalloproteinase (MMP) inhibitors, and angiogenesis inhibitors. For example, compounds such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA) target developing tumor vasculature and have proven useful in cancer treatment when combined with conventional cytotoxic agents. These agents often cause tumor growth inhibition, rather than regression, in animal models. They have better toxicity profiles than cytotoxic drugs and require prolonged administration.

Preclinical Evaluation : Screening of drug candidates for anticancer activity is done in several stages, which are designed to create a 'funnel' with reducing number of compounds entering the successive stages of development. This Anticancer Drug Development 61 screening protocol balances the real-life limitations in the number of drug candidates that can be tested in humans each year with the number of potential new drug candidates that show potential for antitumor activity. During preclinical development, novel drug candidates are produced in sufficiently large quantities and tested for their physicochemical, biopharmaceutical, and solid-state properties. These include the evaluation of solubility, stability in the solid state and solution, pH solubility and stability studies,

Clinical Testing : Clinical trials of drug candidates are carried out in three distinct phases: phase I studies to identify safe dose levels and schedules, phase II studies to identify the spectrum of anticancer activity, and phase III studies to compare the NCE with the up-to-then best-available treatment. In addition, post-marketing surveillance phase IV studies continue to monitor drug safety as it is then administered to a significantly greater number of patients. Regulatory involvement is critical at all stages of clinical drug development. An investigational New Drug (IND) application is filed with the U.S. Food and Drug Administration (FDA) before the initiation of phase I studies. At the end of phase II studies, usually a pre-NDA meeting is held with the FDA to discuss the results and the plans for the phase III clinical trials. Upon completion of the phase III studies, a New Drug Application (NDA) is filed with the FDA for the grant of marketing authorization. The potential toxicities

ISBN 978-93-5240-040-9
and early pharmacology of selected compounds are determined in murine allograft or human xenograft mouse models. For example, at the US National Cancer Institute (NCI), new compounds are evaluated for cytostatic or cytotoxic activity against eight cell lines derived from the most common human malignancies. Compounds that show activities in this pre-screen are tested in more detail in a panel of cell lines of the respective tumor type, and subsequently in animal models.

Result and Discussion : Anticancer drug development brings forth unique perspectives and their regulation has evolved to accommodate and address those unique aspects. One key driving force for anticancer drugs is the urgent patient need for the development of new agents and the need to rapidly move the promising agents into clinical trials. Another is the recognition that these agents are dosed to toxic levels, close to the maximum tolerated dose, MTD, with the precept that the side effects of drug therapy would be less threatening to the patient than their disease. Control of clinical toxicity is sought by careful dosing, monitoring, and prompt treatment of toxicity, or drug withdrawal. The regulatory requirements for anticancer compounds focus on drug safety evaluation in preclinical toxicology studies, based on the intended use and mechanism of action of the drug, and the target patient population. As De George et al. point out, in situations where the potential benefits of therapy are the greatest, e.g., advanced, life-threatening disease, the greater risks of treatment toxicity can be accepted and the requirements for preclinical testing can be minimal. Nevertheless, in cases where the patient population is free of known disease, e.g., adjuvant therapy, chemoprevention, or healthy volunteers, the acceptable risks are much less and preclinical evaluation is more extensive. As discussed before, two acute preclinical toxicity studies are required. The first is in a rodent species to identify doses that result in lethality or life threatening toxicities to derive the clinical phase I entry dose.

Conclusion : The clinical application of anticancer drugs brings forth unique perspectives that are evident in their discovery and development. Historical development of cytotoxic compounds, with significant contributions from serendipity, and the currently shifting focus

ISBN 978-93-5240-040-9

on target-based drug discovery is evident in the evolving paradigms of preclinical and clinical evaluation of new drug candidates. Current challenges of anticancer drug development include the significant time and cost involvement, and the low success rates. These have led to increasing efforts of the pharmaceutical industry toward increasing the effectiveness of the drug discovery and development process and to minimize failure of drug candidates at later stages of development. These efforts include development of high throughput preclinical screening methods and biological assays with greater specificity and predictability. These newly synthesized compounds were evaluated at National Cancer Institute, Maryland, USA for their *in vitro* anticancer activity against 60 human cancer cell lines panel derived from various cancer types like Non-small cell lung, Colon, Renal, Leukemia, Melanoma, Prostate, CNS and Brest Cancer. On the basis of preliminary software screening, out of fourteen compounds, one compound (IV) was selected by NCI for *in vitro* anticancer screening. Compounds with cell lines appearing on the negative side of mean graph exhibit high growth inhibition (GI) of cancer cells of that particular cancer.

References :

1. Barar F.S.K., Essential of Pharmacotherapeutics, 2000. S. Chand & Company LTD., New Delhi.
2. http:/nci. (National Cancer Institute)
3. I. Hutchinson, M.Chua, H. I. Browne, V.Trapani, T. D. Bradshaw, A. D. Westwell and M. F. G. Stevens, J. Med. Chem., 2001,44,1446.
4. Catriona G.M., Wells G., Crochard J.P., Stone E.L., Bradshaw T.D., Stevens M.F.G., Westwell A.D., 2005, J.Med.Chem.,.
5. Sirockin G. and Cullimore S., Practical Microbiology, 1969, Mc Graw Hill Publishing Co. Ltd., Londan,
6. Lorian V., Antibiotics in Laboratory Medicine, 1986 William and Wilkins, Baltimore,
7. Pleczer M. J. Reid R.D. and Chan E. C. S., Microbiology, 1978, Tata Mc Graw Hill Publishing Co. Ltd., London.
8. Schwartsmann G, Winograd B, Pinedo HM. The main steps in the development of anticancer agents. Radiother Oncol 1988; 12: 301–313.