IJPSR (2015), Vol. 6, Issue 1 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 02 May, 2014; received in revised form, 06 August, 2014; accepted, 29 August, 2014; published 01 January, 2015

RECENT INNOVATIVE APPROACHES TO ENHANCE THE EFFICACY AND SAFETY OF ANTICANCER DRUGS: A COMPREHENSIVE REVIEW

Rishi Kant Pandey*, Amit Bihan, Rajul Rastogi and Hans J. Gamperl

Department of Global Vigilance, Fresenius Kabi Oncology Ltd., Echelon Institutional Area, Plot No-11, Sector-32, Gurgaon Pin Code-122001, Haryana, India.

Keywords:

Innovative cancer therapies, radiotherapy, complementary approaches, Targeted therapy

Correspondence to Author:

Rishi Kant Pandey

Senior Research Scientist, Department of Global Vigilance, Fresenius Kabi Oncology Ltd., Echelon Institutional Area, Plot No-11, Sector-32, Gurgaon Pin Code-122001, Haryana, India.

E-mail: rishikant.pandey@fresenius-kabi.com

ABSTRACT: Developing innovative delivery strategies remains an ongoing task to improve both efficacy and safety of drug-based therapy. Anti-cancer drug treatment is seriously affected by various undesirable properties such as poor solubility, narrow therapeutic index and efflux transporter specificity. One of the primary aspects of a successful cancer treatment regimen is to deliver sufficient amounts of drug to tumors while minimizing damage to normal tissues. In this review we highlight the development of promising recent innovative approaches that will hopefully offer not only gains in efficacy, but also in safety, tolerability and convenience in the treatment of patients with cancer. Drug delivery remains a challenge in management of cancer. Approximately 12.5 million new cases of cancer are being diagnosed worldwide each year and considerable research is in progress for drug discovery for cancer. Cancer drug delivery is no longer simply wrapping up cancer drugs in a new formulation for different routes of delivery. The focus is on targeted cancer therapy. The newer approaches to cancer treatment not only supplement the conventional chemotherapy and radiotherapy but also prevent damage to normal tissues and prevent drug resistance. Innovative cancer therapies are based on current concepts of molecular biology of cancer. These include antiangiogenic agents, immunotherapy, bacterial agents, viral oncolysis, targeting of cyclic-dependent kinases and tyrosine kinase receptors, antisense approaches, gene therapy and combination of various methods. Important methods of immunotherapy in cancer involve use of cytokines, monoclonal antibodies, cancer vaccines and immunogene therapy.

Introduction: Innovative treatment approaches to diseases are revolutionizing clinical paradigms with the aim of providing therapy tailored not only to the individual and disease but also within disease sub-types. One of the primary goals of a successful cancer treatment regimen is to deliver sufficient amounts of drug to tumors while minimizing damage to normal tissues.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(1).42-49

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(1).42-49

Most chemotherapeutic agents enter normal tissues in the body with indiscriminate cytotoxicity and do not preferentially accumulate at tumor sites [1, 2]. At times the dose reaching the tumor may be as little as 5% to 10% of the doses accumulating in normal organs.

One reason for the inability for drugs to accumulate at target sites is that the interstitial fluid pressure (IFP) in solid tumors is higher than in normal tissues, that blocking transcapillary transport of chemotherapeutic drugs or antibodies. In this way, the anticancer effect is decreased and toxic effect to normal cells is increased. Probability of severe side effects to the patients often limits the dose of anticancer drugs that can be given to a patient. To

be of clinical interest a drug must provide measurable advantages to patients or to national health services. In other words, it should be more effective than placebo or any other effective treatment; if there is no advantage in term of efficacy, it should at least be safer, more tolerable, easier to use or cheaper than its comparators. Outcome measures should be objective, ultimately establishing the rate of survival and/or the quality of life [3, 4].

MATERIALS AND METHODS:

Only secondary data source i.e. literature review are useful for this review articles. This secondary data source includes: Literature Review- that covered academic journals, trade journals. Internet using the web page content likes FDA, EMEA, TPD and CDSCO. The literature was collected using numerous search engines as Google, Google Scholar, Pubmed, Science Direct etc. for new innovative approaches. Online books & Articles were good source of information.

RESULTS AND DISCUSSION:

Various Recent Techniques and Innovations:

Targeted therapy

The continuous identification of novel alterations result in the elucidation of the mechanisms leading to cancer transformation, growth, invasion and metastasis and the definition of the critical targets of therapy in each of these processes. Even though each cancer is expected to have its own spectrum of signature mutations, some aberrations in signalling appear in a broad range of cancers. These are attractive targets for drug development, because they should be widely applicable.

The new targets included growth factors, signalling molecules, and cell-cycle proteins, modulators of apoptosis and molecules that promoted angiogenesis.

At present, two main approaches are available for use in clinical practice of specific molecular targeting: therapeutic monoclonal antibodies (mAbs) - that deplete the tumour of growth factors or block growth-factor- receptor inter-actions - and small-molecule agents that target various stages in the transduction of the growth signal and its execution[5, 6].

Approaches of Targeted therapy

Prodrugs

A new approach for the delivery of cytotoxic agents to solid tumors is described in which monoclonal antibodies are used as carriers for enzymes to tumor cell surfaces. The enzymes are chosen for their abilities to convert relatively non cytotoxic drug precursors (prodrugs) into active anticancer drugs. The drugs thus formed can then penetrate into nearby tumor cells, resulting in cell death. A number of prodrugs have been developed that can be transformed into active anticancer drugs by enzymes of both mammalian and non mammalian origin.

The enzymes have been shown to localize into tumors when linked to monoclonal antibodies that bind to tumor-associated antigens. *In-vivo* studies indicate that MAb-enzyme/prodrug combinations can result in antitumor activities significantly greater than those of the prodrugs or drugs given alone. This is most likely due to the generation of large amounts of active drug at the tumor site. Alkaline phosphatase (AP) was used to convert etoposide phosphate (EP) into the clinically approved anticancer drug, etoposide. Other drug derivatives, including mitomycin phosphate (MOP) and doxorubicin phosphate (DOP), were subsequently prepared as potential prodrugs that could be activated by AP [7, 8].

Approaches using deactivated drugs are known as gene-directed enzyme prodrug therapy (GDEPT). In the first step, a gene encoding a foreign enzyme is delivered to the tumor for expression. In the second step, a prodrug is administered that can be activated to release a cytotoxic drug by the enzyme that has been expressed in the tumor. Two GDEPT systems that have been investigated extensively are the herpes simplex virus thymidine kinase–ganciclovir (HSV-TK–GCV) combination, and the cytosine deaminase – 5-fluorocytosine (CD–5-FC) combination; both have been tested in clinical trials [7, 8].

Inhibition of angiogenesis

Angiogenesis, the formation of new blood vessels, plays a critical role in tumor progression. There are multiple steps involved in tumor angiogenesis. Each step provides an opportunity for therapeutic

intervention. Although the cellular and molecular mechanisms that govern angiogenesis are only beginning to be understood, it is clear that a balance of pro-angiogenic and anti-angiogenic factors control the formation of new blood vessels. Amongst these factors, vascular endothelial growth factor (VEGF) is one of the most critical and specific angiogenesis factors.

The biological function of VEGF on endothelial cells is mainly mediated through binding to receptor tyrosine kinase, VEGF receptor 1 (flt1/VEGFR1) and VEGF receptor 2 (KDR/flk1/VEGFR2), both are crucial for normal vascular development. Binding of VEGF to VEGFR induces conformational changes in the receptor, followed by dimerization and autophosphorylation of the tyrosine residues of the receptor. Inhibiting VEGF activity by neutralizing antibodies or introduction of dominant negative VEGF receptors. The discovery of the vascular endothelial growth factors and their receptors led to the development of an array of endogenous and synthetic antiangiogenic products. Gene therapy is one of important methods of delivering antiangiogenesis agents with the potential of sustained expression[9].

The first monoclonal-antibody inhibitor of angiogenesis, Avastin® (bevacizumab), was approved by the Food and Drug Administration (FDA) in 2004. This approval was based on the survival benefit observed in a randomized Phase III trial of first-line treatment of metastatic colorectal cancer. In that trial, bevacizumab, a humanized monoclonal antibody directed against VEGF, was combined with conventional chemotherapy. Bevacizumab therapy also increased overall survival in the first-line treatment of advanced non-small-cell lung cancer when used in combination with standard chemotherapy. In addition to being approved by the FDA for use in patients with metastatic colorectal cancer, bevacizumab is approved for patients with unresectable or recurrent non-squamous non-small cell lung carcinoma. It is also being tested in clinical trials for the treatment of a number of other tumor types [10, 11].

Two other antiangiogenic drugs, Nexavar® (sorafenib) and Sutent® (sunitinib), have also been approved by the FDA; these are oral small-molecule receptor tyrosine kinase inhibitors [10, 11.]

Apoptosis (Normal Cell Death)

Apoptosis, or programmed cell death, is a normal component of the development and health of multicellular organisms. Cells die in response to a variety of stimuli and during apoptosis they do so in a controlled, regulated fashion that has attracted considerable attention as the mechanisms involved have become clearer. Drugs that increase apoptosis or antagonize factors responsible for antiapoptotic activity, such as survivin, are of interest for combination therapy. Retinoids are credited with apoptotic activity in addition to their cytodifferentiating activity. HGS-ETR1 (mapatumumab) and HGS- ETR2 (lexatumumab) are examples of apoptosis-inducing therapies. Both drugs are monoclonal antibodies[11, 12, 13].

Radio immunotherapy

Monoclonal antibodies can be chosen for their ability to target specific receptor proteins on the outside of cancer cells and then be modified to also deliver lethal molecules to these cancer sites. Radioactive isotopes can be attached—or conjugated—to carefully chosen monoclonal antibodies. When the conjugated antibody binds to a specific target on the cancer cell's surface, the radiation will fatally damage the cell [14, 15, 16]. Bexxar® (tositumomab) is an example of a radioactive immunotoxin. It is a monoclonal antibody that binds to CD20. Radioactive iodine attached to the antibody releases high doses of radiation that will kill the cell [14, 15, 16, 17, 18].

Immunotoxin Therapy

Monoclonal antibodies can also be conjugated to other types of molecules that are toxic to cells. Mylotarg® (gemtuzumab) is a monoclonal antibody that binds to a protein called CD33. CD33 is on the surface of cancer cells of almost all patients with acute myeloid leukemia (AML) [14, 15, 16, 17, 18].

Epigenomic Targets: New Targets

Unlike genetic changes in cancer, epigenetic changes are potentially reversible. In cultured cancer cell lines, it has been possible for years to re-express genes that had been silenced by

methylation by using DNA-demethylating agents. When given to patients at low doses, these drugs have shown a significant antitumoral activity, and the FDA has approved the use of two such agents, 5-azacytidine and 5-aza-2'-deoxycytidine, as elective treatments for a pre-leukaemic disease, myelodisplastic syndrome. HDAC (Histone Deacetylase) inhibitors constitute another promising group of agents for the epigenetic therapy of cancer. The pleiotropic nature of these inhibitors raises the possibility that their well-known abilities to induce differentiation, cell-cycle arrest and apoptosis are accompanied by other less desirable outcomes.

However, many phase I clinical trials indicate that HDAC inhibitors are well tolerated and, recently, the first drug of this type, suberoylanilide hydroxamic acid (SAHA), has been approved by the FDA for the treatment of cutaneous T-cell lymphoma. The loss of monoacetylated H4K16 can be reversed by a new class of drugs that inhibit sirtuins, the specific subclass of HDACs that deacetylate H4K16. The ability of sirtuin inhibitors to restore the expression of epigenetically silenced tumour-suppressor genes would make this class of drugs of high interest for potential clinical use[19].

Other Recent Approaches:

Chemoprevention

Chemoprevention is gaining importance in relation to the role of nutrition in cancer prevention. Every person is at risk of genetic mutations that lead to cancer. Due to endogenous and exogenous factor every human body has undergone genetic alterations. The time period for first initiated cell to the time of cancer is estimated to be approximately 20 years.

Cancer prevention trials are research studies designed to evaluate the safety and effectiveness of new methods of cancer prevention or screening. The focus of cancer prevention research involved chemoprevention (including vaccination), screening, genetics and lifestyle changes (exercise tobacco cessation) [20, 21]. Numerous studies indicate a relationship between increased consumption of fruits and vegetables and lowered risk of certain cancers. The protective effect from fruits and vegetables may be attributable to multiple factors, including fiber, antioxidants, and other anticarcinogenic compounds. In addition, high fruit and vegetable intake is associated with lower risk of other chronic illnesses, such as cardiovascular disease and stroke [20, 21].

A long list of compounds with different chemical structures isolated from various kinds of vegetables counteract the effect of carcinogenic agents by different mechanisms, including activation of cytochrome *P*-450 and transport proteins such as P-glycoprotein (PgP) [21,22].

Cancer vaccines

Cancer vaccines are designed to boost the body's natural ability to protect itself, through the immune system, from dangers posed by damaged or abnormal cells such as cancer cells. The U.S. Food and Drug Administration (FDA) has approved two types of vaccines to prevent cancer: vaccines against the hepatitis B virus, which can cause liver cancer, and vaccines against human papillomavirus types 16 and 18, which are responsible for about 70 percent of cervical cancer cases. The FDA has approved one cancer treatment vaccine for certain men with metastatic prostate cancer. Researchers are developing treatment vaccines against many types of cancer and testing them in clinical trials [23, 24].

Virotherapy

Virotherapy is another concept involving the use of oncolytic viruses that grow selectively in tumor cells to treat cancer. Viruses that replicate selectively in tumor cells and do not replicate in normal cells are used as agents to fight cancer. Taken as drugs, viruses have some unique properties. They respond to absent molecular targets such as missing IFN or tumor suppressor pathways.

Inactivation of oncogenes by conventional drugs is seldom enough to stop cancer because lack of tumor suppressors is central to cancer progression. In addition a conventional drug does not amplify itself and is needed at very high concentrations to reach all tumor cells. Among different oncolytic viruses adenovirus is the most popular. Virotherapy works against cancer by a combination of different mechanisms. A virocentric point of view considers

the direct lysis of tumor cells by the oncolytic virus as the most important parameter for efficacy[25].

Immunocentrics consider that the lysis of tumor cells is important as long as it can activate an immune response against the tumor. For virocentrics it is important to inhibit the immune response, for immunocentrics is important to boost it even it will neutralize the virus. Probably a combination of these two mechanisms contributes to virotherapy with more or less success depending on the architecture and immunogenicity of each tumor[26].

In general terms, RNA viruses replicate in the cytoplasm and they show faster replication cycles than DNA viruses. The tumor -selective replication of RNA viruses is based on their sensitivity to be inactivated by interferon (IFN). IFNs (alpha, beta and gamma) are secreted by infected fibroblasts and T lymphocytes and bind to specific receptors that trigger a virus-resistant phenotype in surrounding cells. The main mediator of this resistance phenotype is the Protein Kinase R (PKR).

PKR is an IFN-induced serine/threonine protein kinase that, upon binding to dsRNAs produced during virus replication; it phosphorylates the eIF-2-alpha translation factor and leads to shut-off of protein synthesis in infected cells. Besides this antivirus role, IFNs have also antitumor activity. IFNs inhibit cell proliferation by inducing p21 and p202 expression and downregulating c-myc expression; they inhibit caspases and enhance antigen presentation by inducing MHC expression.

Tumor cells with a truncated INF-pathway or an enhanced protein translation escape to such antitumor activity of IFNs and are selected. This characteristic defect of the IFN pathway on tumor cells explains the tumor-selective replication of some IFN-sensitive RNA viruses such as Reovirus, Newcastle Disease Virus an Vesicular Stomatitis Virus.

On the other hand, several RNA and DNA viruses express RNAs or proteins that can inhibit IFN function and the deletion of those genes make them tumor-selective. For example, VAI an VA-II RNAs of adenovirus bind to protein Kinase R (PKR) and inhibit the IFN response to adenovirus [25, 26].

Complementary Therapies: Innovative Approaches to Optimize Standard Therapy

Complementary therapies are recommended to support and optimize the scientifically-based cancer standard treatment. Complementary medicine is currently widely debated by the oncological community, because the required scientific proof of safety and effectiveness for most of the therapeutic approaches has not yet been definitively provided.

In the past years, basic research and clinical evaluation of defined complementary therapeutic concepts in oncology have been intensified in an attempt to integrate these procedures into evidence-based medicine. Complementary approaches in oncology that are recommended as additional to standard cancer destructive therapies claim to optimize this therapy.

Nutrition

The National Cancer Institute (NCI) of the United States attributes about 35% of all types of cancer to malnutrition. The potential for prevention of cancer is thus large and general nutrition guidelines for primary and secondary prevention are of much value, according to the German Society of Nutrition (DGE) and the International Society for Nutrition and Cancer. It is striking to see that both fruit and vegetables play a prominent role in the prevention of cancer [27].

Exercise; Physical Activity

Exercise in the form of “moderate endurance training” (such as walking, jogging, swimming and cycling, all under strict aerobic conditions) and “focused gymnastics” (such as stretching, functional, water, spinal column gymnastics) have proved to be beneficial in the prevention and follow- up of cancer as well as during cancer destructive therapies.

Recently published clinical studies (RCTs, representing level I of the Evidence-based Medicine classification) proved the beneficial effects of moderate endurance exercises to cancer patients in the follow-up period enhanced quality of

life and during standard therapies significantly reduced frequency and severity of fatigue syndrome and other therapy related adverse reactions) [28,29].

Psycho-oncological Support

Psychotherapy is an integral part of acute and rehabilitative treatment in oncology and it has proved its beneficial effects (for example improvement of quality of life and prolongation of disease free intervals) especially for breast cancer patients in well designed RCTs. Psycho-oncological treatment options (such as visualization, relaxation, creativity training and discourse) should be recommended individually and have recently been published[30].

Phytotherapy

Treatment with mistletoe extracts is the most common complementary therapy in Central European oncology. Mistletoe extracts are used as complementary treatment in addition to chemotherapy and radiation treatment and show immunostimulatory, cytotoxic and pain-relieving effects. Mistletoe extracts are generally well tolerated and do not show any toxic reactions even in highly dosed, long-term therapy in cancer patients[31].

Aromatherapy

Aromatherapy is a popular complementary therapy within oncology settings and is known to help relieve patients' anxiety. A new method of delivering aromatherapy to patients was adopted by a complementary therapy service at a UK hospital; aromasticks are similar in design to the Vicks Vapour Inhaler, with the intention of helping patients manage anxiety, nausea and sleep disturbance. Patients referred to the complementary therapy service were, if appropriate, offered an aromastick.

If the offer was accepted patients' details were captured on an evaluation form. One week later the patients were followed up by a different therapist. Frequency of using the aromastick and perceived benefits were documented. A total of 160 patients were included in this evaluation. Aromasticks represent a tool patients can use to self-manage their own symptoms and help them retain an internal locus of control [32, 33].

Recent advances in radiotherapy

The delivery of radiotherapy has changed significantly over the last few decades. We have moved from conventional radiotherapy using simple rectangular treatment fields to increasing conformal radiotherapy techniques such as Image-guided Radiation Therapy (IGRT) and intensity modulated radiotherapy (IMRT).

Intensity modulated radiotherapy (IMRT)

IMRT is an advanced approach to 3-D planning and conformal therapy. It optimizes the delivery of irradiation to irregularly-shaped volumes and has the ability to produce concavities in radiation treatment volumes. When treating head and neck cancers, IMRT allows for a greater sparing of normal structures such as salivary glands, upper aero-digestive tract mucosa, optic nerves, cochlea, pharyngeal constrictors, brain stem and spinal cord. Escalation of radiation dose to greater than 68 Gy using hypo fractionation has been shown to improve outcomes in localized carcinoma of the prostate [34, 35, 36].

Image-guided Radiation Therapy (IGRT)

IGRT is a new approach to delivering radiation therapy that allows for more accurate delivery of radiation to the target tissue. IGRT involves imaging during the course of radiation treatment. A computer compares images taken at the time of treatment to images taken during the planning phase. Through this process, IGRT is able to account for changes in the patient's body or position that may shift the exact location of the cancer. This allows increased accuracy of very complex treatment approaches[37].

CONCLUSIONS: Approximately, two thirds of cancer patients will defeat their disease. The combined use of surgery, radiation therapy and chemotherapy accounts for most of cured cases. A high number of novel drugs are in the pipeline awaiting clinical development, meanwhile, novel strategies such as the antiangiogenic approach and virotherapy are reaching the clinical setting. The magnitude of the discovery of new biomarkers as potential targets in cancer therapy has been extraordinary. The future of successful drug

development in oncology depends on innovative and well planned clinical trials initiated and undertaken with the input of oncology experts who can provide key insights in the early stages of clinical development. Through innovative trial design and further improvements in understanding the molecular aspects of disease, further improvements in patient outcomes can be achieved.

ACKNOWLEDGEMENTS: The preparation of this informative document could never have reached the heights or explored the depths without the help, support, guidance and efforts of some important individuals. Firstly, I would like to thank our H.O.D Dr. Hans J Gamperl for providing us this opportunity. His infectious enthusiasm and unlimited zeal have been major driving forces through our preparation at the Fresenius Kabi Oncology Ltd.

We would like to thank our industry reviewer Dr. Rajul Rastogi for his help and support. We especially grateful to our departmental colleagues for their assistance, and useful insights throughout the preparation. Our sincere thanks to all the people who have contributed to and worked on this context and the previous ones during the last one decade.

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How to cite this article:
Pandey RK, Bihan A, Rastogi R and Gamperl HJ: Recent Innovative Approaches to Enhance the Efficacy and Safety of Anticancer Drugs: A Comprehensive Review. Int J Pharm Sci Res 2015; 6(1): 42-49.doi: 10.13040/IJPSR.0975-8232.6 (1).42-49.