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CLINICAL STRATEGIES OF 5-FLUOROURACIL: A PROMOSING APPROACH FOR CARCINOMA THERAPY

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ABSTRACT
5-Fluorouracil has been used for more than 40 years in the treatment of colorectal cancer. 5-Fluorouracilis given intravenously and has been used in a variety of different schedules to determine the optimum dose and mode of administration. Although 5-Fluorouracil in combination with other chemotherapeutic agents improves response rates, but in colorectal cancer 5-Fluorouracil had the greatest impact. Strategies that have been explored to modulate the anticancer activity of 5-Fluorouracil include decreasing 5-Fluorouracil degradation, increasing 5-Fluorouracilactivation and increasing the TS binding activity of FdUMP. Understanding the mechanisms by which 5-Fluorouracilcauses cell death and by which tumors become resistant to 5-Fluorouracilis an essential step towards predicting or overcoming that resistance. Several studies have demonstrated that administration of anti-inflammatory agents decreases the toxicity of conventional chemotherapeutic agents. For example, combining celecoxib with docetaxel decreased hematologic toxicity in patients with refractory metastatic prostate cancer, even though it only slightly decreased the pain index for patients

Key words: Thymidylate Synthetase, aero-digestive tract, Fluoro Deoxyuridine Diphosphate, oxaliplatin, chemoprotection, inducible nitric oxide synthase (iNOS).

INTRODUCTION

5-Fluorouracilis widely used as an antineoplastic, anti-inflammatory, antimicrobial drug and has vast application in treatment of various cancers like colorectal cancer, breast cancers, prostate cancers and cancer of the aero-digestive tract. Chronic inflammation increases the risk for various cancers, indicating that eliminating inflammation may represent a valid strategy for cancer prevention and therapy. This article explores the relationship between inflammation and cancer with an emphasis on epidemiological evidence, summarizes the current use of anti-inflammatory agents for cancer prevention, therapy and describes the mechanisms underlying the anti-cancer effects of anti-inflammatory agents. 5-Flurouracil, an anti-neoplastic agent, has been reported to have antibacterial activity against (Gram-negative bacteria). This activity is considered to be due to an inhibitory action against thymidylate synthetase. Further as reported previously, some antineoplastic agents exhibited synergism with piperacillin, a β-lactam antibiotic.

ANTINEOPLASTIC ACTIVITY

5-Fluorouracilis widely used in the treatment of cancers like colorectal cancer, breast cancer and cancer of the aero-digestive tract[1]. Although 5-Fluorouracil in combination with other chemotherapeutic agents improves response rates, but in colorectal cancer 5-Fluorouracil had the greatest impact. 5-Flurouracil-based chemotherapy improves overall and disease-free survival of patients with resected stage III colorectal cancer. Nonetheless, response rates for 5-Flurouracil-based chemotherapy as a first-line treatment for advanced colorectal cancer are only 10–15%.

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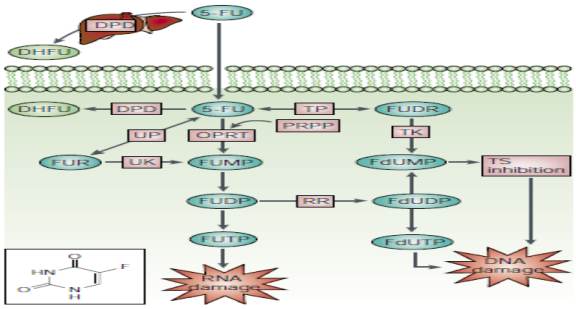
Understanding the mechanisms by which 5-Fluorouracilcauses cell death and by which tumors become resistant to 5-Fluorouracilis an essential step towards predicting or overcoming that resistance.[2]

MECHANISM OF ACTION OF 5-FLUROURACIL

5-Fluorouracilis an analogue of uracil with a fluorine atom at the C-5 position in place of hydrogen. It rapidly enters the cell using the same facilitated transport mechanism as uracil. 5-Fluorouracilis converted intracellularly to several active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridine triphosphate (FUTP). These active metabolites disrupt RNA synthesis and the action of TS. The rate-limiting enzyme in 5-Fluorouracilcatabolism is dihydropyrimidine dehydrogenase (DPD), which converts 5-Fluorouracilto dihydrofluorouracil (DHFU). More than 80% of administered 5-Fluorouracilis normally catabolized primarily in the liver, where DPD is abundantly expressed.

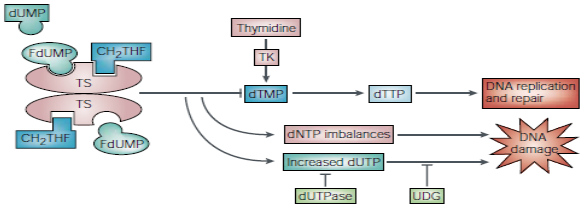


5-Fluorouracil metabolism

5-Fluorouracilis converted to three main active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridinetriphosphate (FUTP). The main mechanism of 5-Fluorouracil activation is conversion to fluorouridine monophosphate (FUMP), either directly by orotate phosphoribosyltransferase (OPRT) with phosphoribosyl pyrophosphate (PRPP) as the cofactor, or indirectly via fluorouridine (FUR) through the sequential action of uridine phosphorylase (UP) and uridine kinase (UK). FUMP is then phosphorylated to fluorouridine diphosphate (FUDP), which can be either further phosphorylated to the active metabolite fluorouridine triphosphate (FUTP), or converted to fluorodeoxyuridine diphosphate (FdUDP) by ribonucleotide reductase (RR). In turn, FdUDP can either be phosphorylated or dephosphorylated to generate the active metabolites FdUTP and FdUMP, respectively. An alternative activation pathway involves the thymidine phosphorylase catalysed conversion of 5-Fluorouracilto fluorodeoxyuridine (FUDR), which is then phosphorylated by thymidine kinase (TK) to FdUMP. Dihydropyrimidine dehydrogenase (DPD)-mediated conversion of 5-Fluorouracilto dihydrofluorouracil (DHFU) is the rate-limiting step of 5-Fluorouracilcatabolism in normal and tumour cells. Up to 80% of administered 5-Fluorouracilis broken down by DPD in the liver.

THYMIDYLATE SYNTHASE (TS) INHIBITION

Thymidylate Synthase catalyses the reductive methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), with the reduced FOLATE 5, 10 methylenetetrahydrofolate (CH_2THF) as the methyl donor. This reaction provides the sole *de novo* source of thymidylate, which is necessary for DNA replication and repair. The 36-kDa TS protein functions as a dimer, both subunits of which contain a nucleotide-binding site and a binding site for CH_2THF. The 5-Fluorouracilmetabolite FdUMP binds to the nucleotide-binding site of Thymidylate Synthase, forming a stable ***ternary complex*** with the enzyme and CH_2THF, thereby blocking binding of the normal substrate dUMP and inhibiting dTMP synthesis.



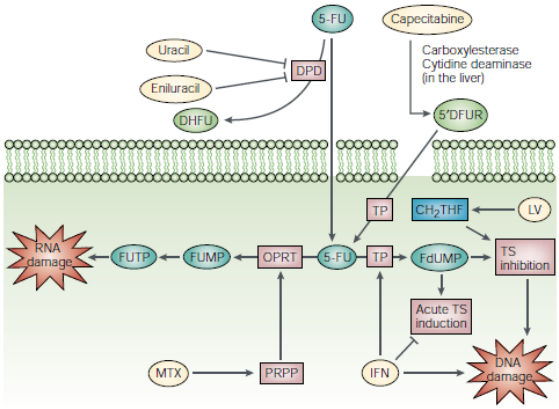
Mechanism of thymidylate synthase inhibition by 5-fluorouracil.

Thymidylate synthase catalyses the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) with 5, 10-methylene tetrahydrofolate (CH2THF) as the methyl donor. The 5-fluorouracil active metabolite fluorodeoxyuridine monophosphate (FdUMP) binds to the nucleotide-binding site of TS and forms a stable ternary complex with TS and CH2THF, blocking access of dUMP to the nucleotide-binding site and inhibiting dTMP synthesis. This result in deoxynucleotide (dNTP) pool imbalances and increased levels of deoxyuridine triphosphate (dUTP), both of which cause DNA damage. The extent of DNA damage caused by dUTP is dependent on the levels of the pyrophosphatase dUTPase and uracil-DNA glycosylase (UDG). dTMP can be salvaged from thymidine through the action of thymidine kinase (TK).

MODULATION OF 5-FLUOROURACIL

5-Fluorouracilhas been used for more than 40 years in the treatment of colorectal cancer. 5-Fluorouracilis given intravenously and has been used in a variety of different schedules to determine the optimum dose and mode of administration. The overall response rate for 5-Fluorouracilas a single agent in advanced colorectal cancer is quite limited (approximately 10–15%). However, over the past 20 years, important modulation strategies have been developed to increase the anticancer activity of

5-Fluorouraciland to overcome clinical resistance. As a result, 5-Fluorouracilhas remained the main agent for the treatment of both advanced and early-stage colorectal cancer. Strategies that have been explored to modulate the anticancer activity of 5-Fluorouracilinclude decreasing 5-Fluorouracil degradation, increasing 5-Fluorouracil activation and increasing the TS binding activity of FdUMP.



Modulation of 5-fluorouracil activity

Leucovorin (LV) increases the intracellular pool of 5, 10-methylene tetrahydrofolate (CH2THF)[3], thereby enhancing thymidylate synthase (TS) inhibition by fluorodeoxyuridine monophosphate (FdUMP). Eniluracil and uracil inhibit DPD-mediated degradation of 5-Flurouracil. Methotrexate (MTX) is thought to increase 5-Fluorouracilactivation by increasing phosphoribosyl pyrophosphate (PRPP) levels. Interferons (IFNs) have been reported to enhance thymidine phosphorylase (TP) activity, abrogate acute TS induction caused by 5-Fluorouraciltreatment and enhance 5-Flurouracil-mediated DNA damage[4]. Capecitabine is a 5-Fluorouracilpro-drug that is converted to 5′-deoxy-5-fluorouridine (5′DFUR) in the liver by the sequential action of carboxylesterase and cytidine deaminase. 5′DFUR is converted to 5-Fluorouracilby thymidine phosphorylase.

ANTI-INFLAMMATORY ACTIVITY OF 5-FLUROURACIL

It has been recognized that infections and inflammation are related to cancer, and strong correlations between the presence of inflammation and the development of precancerous lesions at various anatomic sites have been established. Exemplary studies have indicated that there is an approximately 14% increase in prostate cancer risk due to prostatitis, 25% increase in colorectal cancer risk due to ulcerative colitis , and a 10-20 fold increase in the risk of pancreatic cancer for patients who have experienced pancreatitis.[5] Thus, the presence of inflammation appears to induce or facilitate carcinogenesis. Inflammation may lead to the initiation of cancer is reasonable considering that chronic inflammation is characterized by infiltration of mononuclear immune cells (including macrophages, lymphocytes, and plasma cells), tissue destruction, fibrosis, and increased angiogenesis. Increased genomic damage, increased DNA synthesis, cellular proliferation, disruption of DNA repair pathways, inhibition of apoptosis, and the promotion of angiogenesis and invasion are also associated with chronic inflammation . All of these processes have been implicated in the initiation and progression of cancers. During chronic inflammation, pro-inflammatory molecules, such as cytokines, inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), and NF-kB are upregulated. Together, these processes provide a favorable microenvironment for the exponential growth of malignant cells. Thus, inflammation[6] may provide both the key mutations and the proper environment to foster tumor growth. Extensive data demonstrate that inflammation plays a role in the establishment, progression and aggressiveness of various malignancies. As tumor develops, it expresses phenotypes similar to inflammatory cells. For example, numerous cancer cells express cytokines, chemokines and their receptors. Molecular mediators and their respective receptors have a significant impact on angiogenesis, cell migration, and metastasis. In a study, a number of cytokines, including IL-6, IL-8, G-CSF (granulocyte colony stimulating factor), IFN-γ (interferon-γ), and MIP-1β (macrophage inflammatory protein- 1β), were found to be more abundant in breast carcinoma than in normal breast tissue. Surprisingly, the expression level of IL-8, an important regulator of neutrophil activation, chemotaxis and activator of NF-kB, negatively corresponded with estrogen receptor status. The mediator was is more abundant in high-grade tumors than low-grade tumors, increase in tumors that exhibit high macrophage content and increased vascularization. MIP-1β expression was also higher in high-grade breast carcinomas compared to low-grade tumors. Its expression corresponded to B lymphocyte, T lymphocyte, and macrophage infiltration, and was found to correlate with the overall presence of inflammatory cell components. Additionally, the observed levels of AP-1 (activator protein-1), a transcriptional target of NF-kB and known regulator of numerous inflammatory cytokines, correlated with the expression levels.

MECHANISMS OF ANTI-CANCER ACTION OF ANTI-INFLAMMATORY AGENTS

There is evidence that anti-inflammatory agents are effective adjuvants for conventional therapies. Since monotherapy is typically insufficient to eradicate cancer, combination therapy is generally administered. A number of both clinical and preclinical studies suggest that the combined use of anti-inflammatory agents and conventional therapies may improve patient prognosis. Although the underlying mechanisms of action for the

effects of anti-inflammatory agents as adjuvants are not fully demonstrated, three primary modes of action have been proposed: chemoprotection, alterations in pharmacokinetics i.e., metabolism and chemosensitization.

CHEMOPROTECTION BY ANTI-INFLAMMATORY AGENTS

A large number of adverse effects are associated with the various clinically used anticancer agents. The majority of agents target rapidly proliferating cells, resulting in toxicity to both the tumor and various host tissues, primarily the gastrointestinal tract and bone marrow. Other toxicities arise as a result of accumulation of the agent in a particular anatomic region (e.g. the cardiovascular system or liver). These side effects limit the dose of agent that can be given and greatly reduce patient quality of life. The ability to prevent or ameliorate these side effects would improve both the therapeutic response and patient quality of life. Several studies have demonstrated that administration of anti-inflammatory agents decreases the toxicity of conventional chemotherapeutic agents. For example, combining celecoxib with docetaxel decreased hematologic toxicity in patients with refractory metastatic prostate cancer, even though it only slightly decreased the pain index for patients. Similarly, the addition of celecoxib to a FOLFIRI (folinic acid, fluorouracil and irinotecan) regimen decreased the incidence of diarrhea for patients, allowing for administration of higher doses of irinotecan (200mg/m2) than can typically be tolerated. A trial investigating the combination of capecitabine and celecoxib for patients with metastatic breast cancer indicated that the addition of the COX-2 inhibitor decreased the incidence of capecitabine-associated diarrhea and hand-foot syndrome. The recently completed GECO (Gemcitabine-Coxib) study was designed to evaluate the addition of rofecoxib to first-line chemotherapy[7] regimens in patients with advanced non-small cell lung carcinoma (NSCLC).[8] Despite the withdrawal of rofecoxib and the consequent cessation of the treatment, patients receiving adjuvant rofecoxib therapy exhibited higher response rates. Additionally, patients who had undergone at least 3 months of rofecoxib treatment, improved quality of life, measured by decreased fatigue, weight loss, pain, and analgesic consumption are various physiological functions that are experienced. Our own studies have focused on the anti-inflammatory glucocorticoid, dexamethasone. Dexamethasone has been used as an anti-emetic for cancer patients for many years, but has more recently been examined for potential chemoprotective and therapeutic effects. In our studies, we observed that dexamethasone decreased the hematotoxicity of gemcitabine and carboplatin in both CD-1 mice and human NSCLC patients in a dose- and scheduledependent manner. A study in advanced colorectal cancer patients demonstrated that administration of a different glucocorticoid, budesonide, led to a trend toward decreased incidence and duration of diarrhea in patients receiving irinotecan, as well as a diminished need for loperamide rescue .Other NSAIDS, aspirin in particular, may also prove to be beneficial as anti-thrombotic agents if administered in combination with chemotherapeutic modalities. Approximately 90% of cancer patients display hypercoagulability, indicating that co-administration of antithrombotic NSAIDs[9] may aid in preventing arterial thromboses, allowing cytotoxic agents to more easily reach microscopic tumor foci and improve the prognosis of cancer patients. Anti-inflammatory agents may also protect against neurotoxicity by decreasing or inhibiting the disruption of the blood-brain barrier. The cyclooxygenase (I and II) inhibitor indomethacin and COX-1 inhibitor, VAS, prevented disruption of the blood-brain barrier in rats following intracerebral injection of TNF-α. These effects were attributed to both COX inhibition and a decrease in the expression and activity of matrix metalloproteinases (MMPs). Glucocorticoids, including dexamethasone, have also been shown to stabilize the blood-brain barrier, and are frequently used to treat cerebral edema. Dexamethasone may exert its effect by decreasing VEGF and increasing angiopoietin-1. These studies indicate that the use of anti-inflammatory agents may prevent or inhibit many of the dose-limiting toxicities of several of the most commonly used anti-neoplastic agents. Anecdotal evidence suggests that other agents may have similar effects, implying that combination therapy with conventional chemotherapeutic agents and anti-inflammatory agents is an under-investigated area that may yield significant improvements in patient care.

ALTERATIONS IN PHARMACOKINETICS OR METABOLISM

One of the mechanisms responsible for the chemoprotection induced by anti-inflammatory agents is that their administration can change the pharmacokinetics and pharmacodynamics of other therapeutic agents. For example, dexamethasone was shown to protect mice from hematotoxicity in a dose- and schedule-dependent manner. It was demonstrated that the drug altered the pharmacokinetics of carboplatin, gemcitabine and doxorubicin in both CD-1 mice and in a variety of mouse xenograft cancer models. While there were no major differences in the plasma pharmacokinetics of carboplatin or gemcitabine in mice pretreated with dexamethasone, there were significant decreases in their uptake by the spleen and bone marrow, accompanied by decreases in AUC (area under the curve), T1/2 (half-life) and Cmax (maximum concentration), as well as an increase in clearance of the drugs . More importantly, when animals were pre-treated with dexamethasone, the AUCs of the chemotherapeutic agents in the tumor were increased, while the AUCs in the bone marrow and spleen decreased. Similar effects were observed when dexamethasone was

combined with adriamycin in a syngeneic model of mammary cancer. Thus, administration of the glucocorticoid can alter the pharmacokinetics of chemotherapeutic agents to decrease their toxicity and increase their activity in the tumor. Even when the anti-inflammatory agents do not affect the pharmacokinetics of the chemotherapeutic agent, they may alter its metabolism, leading to differences in the concentration, half-life, and clearance of the active metabolite, thus altering the toxicity and efficacy of the agent(s). For example, several agents, including rofecoxib and mefenamic acid, are potent inhibitors of CYP1A2. Dexamethasone is an inducer of CYP2D6, while celecoxib inhibits the activity of the enzyme. It is possible that by affecting CYP2D6 activity, dexamethasone or celecoxib may alter the efficacy of tamoxifen (which is metabolized by CYP2D6) treatment for preventing breast cancer recurrence. Other mechanisms by which the anti-inflammatory agents can alter metabolism of chemotherapeutic agents are also possible. Another NSAID, diclofenac, inhibited the metabolism of the novel chemotherapeutic agent DMXAA in mice by preventing its glucuronidation, leading to increased plasma AUC and decreased clearance. Another factor influencing the amount of drug reaching the tumor is the tumor interstitial fluid pressure (IFP). Most tumors have high IFP, most likely resulting from abnormal vasculature or lymph vessels, or fibrosis of the surrounding stroma. This high pressure acts as a barrier to drug delivery to the tumor from the circulation, preventing therapeutic agents (most of which have relatively high molecular weights) from entering tumor cells. Various studies have demonstrated that high IFP correlates with a worse prognosis and decreased response to therapy. Several approaches have been shown to lower IFP, including VEGF and PDGF antagonists and dexamethasone. In our studies, we observed an increased uptake of chemotherapeutic agents by xenograft tumors following pre-treatment with dexamethasone. This effect may have been due to the change in tumor IFP. Another study indicated that there was a trend toward reduced tumor IFP in patients treated with celecoxib. Thus, changes in the distribution or metabolism of chemotherapeutic agents can be induced by prior or co-administration of anti-inflammatory agents. While these changes can be deleterious under many conditions, it is also possible (as in the case of dexamethasone) to use these changes to protect normal tissues from toxicity or to increase the efficacy of a particular chemotherapeutic agent. Special care must be taken for studies that target differences in metabolism to ensure that all patients have metabolic enzymes that function at normal levels. Polymorphisms in the cytochrome p450 enzymes are common, and may lead to unexpected changes in toxicity or efficacy of both chemotherapeutic and anti-inflammatory agents.

ANTIBACTERIAL ACTIVITY OF 5-FLUOROURACIL

5-Fluorouracil has been reported to have antibacterial activity against Gram-negative bacteria. This activity is considered to be due to an inhibitory action against thymidylate synthetase. One of the most common complications involved in treating patients with hematologic cancer is infections. In many cases there are multiple factors that predispose patients to infections such as neutropenia induced by therapy or bone marrow involvement, hypogammaglobulinemia, T-cell dysfunction, and mucosal damage. The spectrum of infections has changed with the use of purine analogs and the advent of monoclonal antibodies. Gram-positive organisms account for 60% to 70% of microbiologically documented. Staphylococcus aureus is one of the most frequently pathogens cause infections especially in hematological and oncological patients with febrile neutropenia. Antineoplastic drugs used for treatment of malignant diseases and affect all cells with rapid turnover. The mechanism of action is inhibition of production of DNA and RNA by inhibiting formation of purine and pyrimidine. Several antineoplastic drugs are known to have antibacterial effects. The previous studies revealed bactericidal effect of antineoplastic drugs which used for treatment of leukemia on intestinal and oral flora. 5-Fluorouracil was found to inhibit strains of Staphylococcus aureus in low concentration. Bactericidal effect (synergisms & antagonisms) of combinations of antibiotics and antineoplastic drugs commonly used in clinical practice to certain bacteria were detected. The aim of this study is to reveal the antibacterial effect of some antineoplastic drugs used for treatment of leukemia on clinical isolates of Staphylococcus aureus isolated from UTI cases in leukemic and non-leukemic children and to detect the occurrence of synergism and antagonism between antibiotics and these drugs.

MATERIALS AND METHODS

Bacteria: Twenty isolates of Staphylococcus aureus were isolated from samples of urinary tract infections in children (7-15 years males & females). Ten of these isolates from children suffering from leukemia (in addition to UTI) under chemotherapy.[10] The isolates were identified according to Diagnostic microbiology. Antibacterial activity of each of antineoplastic drugs and antibiotics against Staphalococcus aureus were tested on Mueller Hinton agar by disc diffusion method. Antineoplastic disc prepared in a concentration 25 & 50 µg. The activity of combinations of antibiotics and antineoplastic drugs (synergism & antagonism) were initially screened by disc diffusion method. A big disc (30 mm diameter) saturated with sub-MIC of antineoplastic drugs placed in the dish center and antibiotic discs were placed around it. Appearance of clear zone between the central disc and any of antibiotic disc recorded synergism. Minimal inhibitory

concentration (MIC) is done by microtitration method; two ranges of two fold serial dilutions were prepared. Dilutions were made from 18 hour. Cultures of Staphalococcus aureus to results approximately 106 CFU/ml. The wells were inoculated with 0.1 ml of bacterial suspension. The effect of antineoplastic drugs on hemolysin production (activation or inhibition) was done on blood agar by adding antineoplastic disc on lines of bacterial growth.

RESULTS

Results of antibacterial activity test of antineoplastic drugs showed completely resistance of Staphalococcus aureus which was isolated from leukemic children to all of these drugs, while the isolates from children suffering from UTI only showed sensitivity to 5-fluorouracil with inhibition zone more than 18 mm diameter. Minimal inhibitory concentration values of antineoplastic drugs for isolates from leukemic children were higher than that for other isolates from non-leukemic children. Antibiotic susceptibility test revealed high resistance percentages to antibiotics by isolates from leukemic children comparing with other isolates and three isolates were resistant to vancomycin.

MICS VALUES (µG/ML) OF ANTINEOPLASTIC DRUGS FOR STAPH AUREUS ISOLATES

ISOLATES SOURCE	DRUG (µg/ml)
Leukemic children (10 isolates)	64
Non leukemic children (10 isolates)	8

DISCUSSION

The study correlates the global gene expression in a panel of 85 cancer xenografts with chemosensitivity to nine anticancer agents including 5-Flurouracil. They established an algorithm that calculated a drug sensitivity score based on the expression of a subset of genes that correlated with drug sensitivity. This study consistently revealed an inverse correlation between TSmRNA levels and 5-Fluorouracilsensitivity. In addition, the expression levels of mRNAs encoding the multidrug resistance proteins MDR3 and MDR4 were found to significantly correlate with 5-Fluorouracilsensitivity. Similarly, DNA microarray profiling has been used to predict survival of oesophageal cancer patients given adjuvant chemotherapy. A subset of 52 genes that correlated with prognosis and possibly with sensitivity to 5-Fluorouraciland cisplatin were identified. This study established a drug-response score based on the expression of these 52 genes, which the authors concluded great potential for predicting prognosis. Much emphasis is being placed on investigating new combinations and new regimens for using the anti-inflammatory agents. There are currently at least 98 active clinical trials investigating the use of celecoxib[11] for cancer, most of which are focused on its use in combination with different chemotherapeutic agents and radiation therapy. These trials have the potential to rapidly affect patient c4are, since both the anti-inflammatory and anti-cancer agents/approaches have already been approved for use by the FDA. As such, there are several directions that researchers need to take in order to take advantage of the approval status of these agents.

CONCLUSION

The benefit of combining information from three molecular biomarkers compared with using a single marker has been showed clearly. Increasing the number of biomarkers analysis further increases ability to predict drug response. Therefore transcriptional profiling has excellent potential as a means of prospectively identifying patients who are most likely to respond to chemotherapy. Tailoring treatment according to the molecular phenotype of tumour and patient will result in increased tumour response rates. In addition, patients will be spared the toxic side effects of treatment from which they are unlikely to benefit. Higher response rates and decreased toxicity would also reduce the costs of patient care, whereas expensive treatments, such as oxaliplatin or irinotecan, may be used in a more targeted manner. Future studies may define a set of key marker genes, which might be used for prospective evaluation of tumour response to 5-Fluorouraciland other chemotherapeutic agents. Inflammation has been demonstrated to play a major role in initiation, progression, and prognosis of cancer.[12] The use of anti-inflammatory agents decreases the incidence and recurrence of various cancers and improve the prognosis for patients. Additionally, the use of anti-inflammatory agents in combination with conventional anti-cancer therapies is gaining ground which is likely to yield many new therapeutic approaches to treating cancer within the next decade. Moreover, earlier diagnosis and treatment of inflammatory conditions (e.g. prostatitis, hepatitis, and pancreatitis) may be useful for preventing the initiation of cancer by inflammatory processes. While the currently used, FDA-approved, anti-inflammatory agents undeniably have potent activities, their off-target effects and toxicities have less attractive options for cancer therapy at current doses and dosing frequencies. Thus, new combinations of agent modifications to dosing or frequency or the use of new anti-inflammatory compounds represent the next generation of care for both inflammatory and cancer diseases.

FUTURE CHALLENGES

In recent decades, several anticancer drugs have been approved for the management and treatment of colorectal cancer. These drugs do not represent a revolution in the treatment of colorectal cancer. However, 5-Fluorouracilhas continued to be used for the treatment of tumors and widely employed in clinical chemotherapy[13]

for the treatment of carcinomas of the colorectal region. Nevertheless, its clinical benefits are greatly limited due to drug resistance, which occur from various causes including alteration of drug influx and efflux mechanism, enhancement of drug inactivation and mutations of the drug target. Certainly, many mechanisms of 5-Fluorouracilanticancer potential and drug resistance have yet to be demonstrated. The nano drug delivery technologies may enable practitioners to fabricate 5-Fluorouracil and investigate molecular mechanisms more specifically. Therefore, the urge to seek the better therapeutic strategies to increase 5-Fluorouracil cytotoxicity, sensitivity and reverse resistance to drug are the key tasks in the near future.

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