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Specific Cell-Signal Targets for Cancer Chemotherapy

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Attempts to develop drugs, specific for cancer cells, are dealt here according to the intended cell-target. While many target specific drugs were developed, they reach only moderate successes in clinics for reasons, such as, delivery problem, lack of in vivo efficacy or toxicity. However, recent efforts focusing on the diversity of tyrosine kinases, participating in cell-signal transduction, brought fruit. The firs such drug, Givec, approved by the USFDA recently, is used in clinics with great success to threat CML. The drug inhibits tyrosin kinase of bcr-abl, c-abl and v-abl. Work is progressing on other tyrosin kinase inhibitors and on other type of specific cancer cell signal protein inhibitors. These efforts are hoped to yield better cures for cancer in the near future.

Key words: Chemotherapy, Tyrosine kinases, Signal times duction, Leukemia, epidermal Growth factor

INTRODUCTION

Cancer is one of the leading disease-related causes of death. This lead is increasing due to the fact that humans enjoy an ever increasingly prolonged life span. The occurrence of cancer in the elderly population is increasing because of the accumulation of genetic mutations that manifest in cancerous cell-transformation. Treatment of cancer can be done by several modalities: such as, surgery, radiation, chemotherapy or a combinations of these modalities. The first two modalities may be successful if the cancer is detected at an early time and is localized. If the cancer has progressed to a metastatic stage, chemotherapy is introduced, which is mostly palliative, except in a few cases, such as childhood leukemia and testicular cancer.

Most of current cancer chemotherapeutic treatments are palliative because the applied anti-cancer drugs are inhibitors of cell proliferation and are inherently toxic to normal cells. To avoid such toxicity, specific targets in cancer cells, not present in normal cells, are sought after. Recent advances in molecular biology permit us to identify genes that are specifically overexpressed in cancer but not in normal cells. After initial discovery of oncogens, such as *ras, myc, raf, abl*, etc (Perkins *et al.*, 1997) many other aberrant gene expressions were also associated with cancer. Several gene products, overexpressed in cells, such as HER-2, EGF, telomerase and cyclines, were also associated with some cancers (Shapiro and Harper, 1999). In the case of telomerase, the enzyme which maintains the length of chromosome end-caps (telomers), if it is induced to be overexpressed, along with *ras* and large *T antigene* oncogens, it could transform normal cells to cancerous cells (Hahn *et al.*, 1999). Such discoveries have led to potential "specific" targets for cancer chemotherapy. In general, potential "cancer specific" drug targets relate to signal pathways of cancer cells, which signal pathway targets are absent or not overexpressed in normal cells. Such drug targets are being explored, especially by industry. A "cancer specific" drug is expected to be less toxic to the host than drugs targeting cell proliferation, as mentioned above. Nevertheless, the search for "specific" inhibitors of cancer cells is a difficult task. Such specific inhibitors have to meet pharmacological and toxicological criteria in humans, in addition to "specificity" for the cancer cells.

In this review examples of potential drugs developed with the above aims will be discussed briefly. With the discussed examples, we intend to show the direction of anti-cancer drug development based on recent discoveries in cell signaling mechanisms. Emphases will be on those potential drug candidates which already have reached clinical trials; therefore, where possible, short pharmacokinetics and clinical schedules of the discussed drugs will be provided. However, reaching the stage of

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clinical trials does not mean that the drug candidate will or was approved as a drug. Also, in some important cases, drug candidates which show promise in preclinical testing only, will be briefly mentioned to show possible future directions. Potential drug candidates will be reviewed according to their "specific" targets. This brief review will focus on drugs only and not on biological agents or gene therapy.

DRUG CANDIDATES WITH SPECIFIC CANCER CELL TARGETS

Modulation of protein kinase activity

Protein kinases (PK) play a significant role in relation to second messengers, such as cAMP, Ca^{2+} and inositol phosphates. Therefore, the modulation of PKs, and specifically PKC activity, was a target of cancer research, in the hope of interrupting the proliferation of cancer cells.

One of the promising compounds, 8-chloro adeno-sine 3',5'-cyclic monophosphate (8-Cl-cAMP) was tested in clinical trials. The preclinical laboratory results, which gave the background for the clinical testing, were as follows: Cyclic adenosine monophosphate (cAMP), a second messenger, signals through type I and type II cAMP dependent PKs. The distribution of these type I and type II of kinase is different in normal and malignant cells. It was shown by North et al (North *et al.*, 1994) that 8-Cl-cAMP inhibits the expression of the cAMP-binding regulatory subunit of PKA I (RI) which is associated with cancerous transformation. It also induces a regulatory subunit, PKA II, that can cause cell growth arrest. Also metabolites of 8-Cl-cAMP and an analog, 8-NHZ-cAMP, were shown to induce cell growth arrest in MCF-7 cells (Vintermyr *et al.*, 1995). 8-Cl-adenosine, a metabolite of 8-Cl-cAMP induces apoptotic cell death without DNA fragmentation (Boe *et al.*, 1995). It was speculated that this apoptotic signal works through bcl-x_L rather than bcl-2 (Han *et al.*, 1996).

In vivo experiments confirmed the results of the in vitro experiments. The ratio of PKA isoenzymes changed after 8-Cl-cAMP was administered to animals. In xeno-grafts, the ratio of the regulatory subunits, RI/RII was reduced, as expected. Administration of 8-Cl-cAMP slowed the growth of certain tumors in animals (Ramagr *et al.*, 1995). However, in hormone (estrogen, progeste-rone) dependent tumors, 8-Cl-cAMP additively stimulated proliferation with estrogen receptor stimulation. In hormone independent tumors, 8-Cl-cAMP inhibits tumor growth and therefore this compound was tested in clinical trials, but only with hormone independent tumors, with limited success (Actis *et al.*, 1995).

Another compound, a natural product, bryostatin 1 was shown to activate PKC without being a tumor promoter (Pettit, 1991). Bryostatin 1 activity is synergistic with lipopolisaccharde in releasing TNF-alpha in MONO-MAC-6 cells (Steube and Dexter, 1995). It also induces apoptosis in WSU-DLC2 cells (Mohammed *et al.*, 1995), and together with vincristine it suppresses bcl-2 and increases expression of p53 in synergistic fashion (Maki *et al.*, 1995). Another activity of bryo-statin 1 is the inhibi-tion of cdk2 activity, resulting in the dephosphorylation of this enzyme (Asiedu *et al.*, 1995). Several other activities of bryostatin 1, such as differentiation of chronic lympho-cytic leukemia (CLL) cells were also demonstrated (Dexter *et al.*, 1989). Preclinical toxicological studies in mice revealed that a dose of 75 mg/kg, bryostatin 1 causes kidney and lung tissue necrosis. At tolerated lower doses, the initial lethargy, weight loss and reduced hematocrit normalized after a recovery period. Phase 1 clinical study indicated a usable schedule: 25 mg/m^2, iv, within a 1 h period, once a week for 3 weeks (Philip *et al.*, 1993). Dose limiting toxicity is ayalgia. Recent clinical trials are conducted with lymphocytic leukemia and lymphoma patients. One of the drawbacks of the bryostatin 1 is that it is a substrate of P-glycoprotein. Therefore it is difficult to treat cancers which are resistant to chemotherapy because of the expression of this efflux pump.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors merit specific attention. Recently, the US Food and Drug Administration approved a drug, Glivec, that specifically inhibits tyrosine kinase in chronic myeloid leukemia (CML) cells and therefore has minimal host toxicity (see below).

In general, receptor activated cell signaling is translated via biochemical reactions to the nucleus. Signal translation involves mostly phosphorylation and dephosphorylation of proteins that are related to cell signaling events. Phosphorylations may occur at serine/threonine or at tyrosine sites of proteins. Several phosphorylation events may occur simultaneously, and a cell integrates the signals and proceeds in one of three possible directions: proliferation, cell-death or quiescence. Tyrosine kinase overexpression can result in mutations and persistent cell growth stimulation and ultimately cancer (Bishop, 1995). For these reasons, tyrosine kinase activities were identified as potential targets for drug development. For example, it was established that growth factor stimulation can be transmitted through ras-raf-MAP kinases to cell proliferation (Cobb and Goldsmith, 1995). Therefore, these kinases can serve as targets for drug development. Furthermore, receptor tyrosine kinases may activate phosphoinositid-3-kinases, causing enzyme activity that leads to inositol lipid phosphorylation and in turn activation of PKB

oncogene (Franke *et al.*, 1997).

In studying different tyrosine kinases activities, it was established that these enzymes phosphorylating tyrosine residues in different protein substrates are not identical, and that selective inhibitors could be developed for them. This finding initiated the development of specific tyrosine kinase inhibitors, which tyrosine kinases are specific for certain oncogenic cell signaling (Levitzki and Gazit, 1995). However, one should mention that some cells have different apoptotic sensitivity to different types of tyrosine kinase inhibitors. For example, apoptosis can be induced in non-small lung cancer cells more effectively by tyrosine kinase inhibitors that target Jak2 or src-family kinases than by agents that target the HER family of receptor (Zhang *et al.*, 2001).

Research by the pharmaceutical company, Novartis led to the development of Glivec, as mentioned above. Glivec is a compound composed of aromatic and aliphatic cyclic benzene and nitrogen containing rings, connected by nitrogen and amide linkages. It was shown to be a selective inhibitor of bcr-abl, c-abl and v-abl tyrosine kinases (Druker *et al.*, 1996). Cell culture assays established that Glivec inhibited cell growth of cells which are positive for the Philadelphia chromosome (Beran *et al.*, 1998). The growth of cells expressing PDGF were also inhibited by Glivec, indicating the tyrosine kinase inhibition for this receptor (Caroll *et al.*, 1997). Selectivity of this drug in hematopoietic cell culture was demonstrated. Colony formation of CML cells was almost completely inhibited by 1 microM of the drug while normal hematopoietic cells was not affected (Deninger *et al.*, 1997). Prolonged treatment of bcr-abl expressing cells with Glivec may result in resistance to this drug. The cause of resistance could be overexpression of bcr-abl protein or overexpression of P-glycoprotein. Glivec seems to be a substrate of P-glycoprotein (Mahon *et al.*, 2000). Because of this, oral absorption of Glivec may be affected by other P-glycoprotein drug-substrates in the intestines therefore. Furthermore, simultaneous administration of other drugs, which are also substrates of P-glycoprotein may result in penetration of Glivec into the CNS compartment (Ibrahim *et al.*, 2000).

In vivo testing in mice established the drug's efficacy and a therapeutic dose schedule for the drug (LeCountre *et al.*, 1999). Briefly, bcr-abl positive KU812 cells, obtained from CML patients were xenografted into nude mice. Three times daily administration of 50 mg/kg, iv. or 160 mg/kg po., for 11 days resulted in tumor free survival. Specificity of the in vivo effect of this drug was established by experiments when tumor growth, initiated by bcr-abl-negative cells, was not inhibited by the same treatment in nude mice.

Following the successful preclinical studies, a Phases I study was conducted with CML patients in blast crisis (Sawyer *et al.*, 2000). Dose escalation was from 300 to 1000 mg Glivec daily. Response rate was 23/39, including 13 patients with complete remission. The follow up multicenter Phase II study was conducted with 262 patients, with about half of the patients which were treated previously for blast crisis. After 4 or 8 weeks follow up, the response rate for untreated patients was about 47%, and for patients who received prior therapy for blast crisis, 33 to 38%. Toxicity included neutro-penia, thrombocytopenia, fluid retention and liver function abnormalities, but only in a single digit % of the patient population.

Another drug, Sandostatin (Octreotid), a somatostatin analog, was shown to inhibit epidermal growth factor initiated tyrosine phosphorylation. Other experiments related the receptor-somatostatin complex to growth inhibition by induction of phosphatase activity (Liebow *et al.*, 1989) and to reduction of EGF production (Lamberts *et al.*, 1987). Since EGF-1 and EGF-beta may be involved in some tumor growth, the use of somatostatin analogs to suppress tumors expressing endocrine factors seemed plausible. Clinical trials started with patients with colorectal, small cell lung and pancreatic cancers. It was found that octreotide distributed rapidly after iv. or sc. administration and that its half-life is about 1.5 h. Treatment of granulated pituitary adenoma with 300 mg/m^2/day octreotide reduced the level of growth hormone about 30%. This treatment combined with surgery achieved further reduction of production of growth hormone (Ezzat *et al.*, 1995). Another treatment modality, ex vivo treatment of cells from acute lymphoblastic leukemia and acute myelolitic leukemia (AML) patients with octreotide showed some success as measured by cell growth arrest (Santini *et al.*, 1995).

Flavopiridol, a drug studied for some time, directly inhibits tyrosine phosphorylation. Proliferation of breast, lung and prostate carcinoma cells could be arrested with flavopiridol without affecting cells in stationary phase (Kaur *et al.*, 1992). Flavopiridol was found to specifically block phosphorylation of p34/cdc2 kinase without inhibiting p34/cdc2 expression. In vivo flavopiridol retards xenografted colorectal and prostate tumors in mice with limited bone marrow toxicity following bolus administration. Dividing the effective dose into multiple daily doses, minimizes toxicity but keeps efficacy. Further clinical trials should determine the usefulness of this drug. In vitro, combination of flavopiridol with sodium butyrate, a cell differentiation agent (see below), caused disruption of the expression of $p21^{waf\text{-}1,CIP1}$ and enhanced apoptosis in human myeloid leukemia cells. The combination induced caspase-mediated cleavage of cdkI $p27^{CIP1}$, pRB and the anti-apoptotic protein, bcl-2. This finding demon-strates that co-administration of a differentiation inducer with a cycline-dependent kinase inhibitor can initiate strong apoptotic cascade (Rosato *et al.*, 2001).

Another specific inhibitor of tyrosine kinase, OSI-774, targets the EGF receptor and is in clinical development (Malik *et al.*, 2001). Head and neck squamous carcinomas expressing this receptor were treated with OSI-774 at a dose of 150 mg/day for 28 days, po. Significant changes in the phosphorylation of EGF receptor downstream signaling proteins, Akt and ERK, and could be demonstrated in tumor biopsies of patients.

Receptor antagonists

Platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) can drive cells to proliferation (Antoniades *et al.*, 1992; Yoshida *et al.*, 1993). Blocking these receptors may suppress tumor growth. A compound, SU101, trifluoro-5-methyl-4-isoxazol carboxy-p-toluid, was found to inhibit cell growth of several established ovarian, prostate and leukemia cell lines. These cell lines express receptors for PDGF and VEGF (Mason *et al.*, 1996). The drug inhibited human glioma and glioblastoma cells xenografted into BALB/c nude mice at a daily dose of 15-20 mg/kg, ip. The useful dose regiment in the clinic proved to be the same dose infused over 24 h period/week for 4 weeks. The metabolite of this drug is eliminated in about 320 h, dose dependently. Therefore, this long clearance time permitted infrequent administration of this drug.

Many other receptor antagonists have been studied recently. For example, several years ago antibodies against HER2-New tyrosine kinase receptor proved to be effective in breast and ovary carcinomas in clinical trials (Bacus *et al.*, 1992). The antibody blocked receptor tyrosine phosphorylation and no stimulatory signal was transmitted. A compound with tyrphostin structure, inhibitory to EGF tyrosine kinase, inhibited the growth of human squamous cell carcinoma xenografed into nude mice (Yoneda *et al.*, 1991). These receptor antagonists are still under development.

It is interesting to mention a study, which demonstrated that constitutively expressed HER2 tyrosine kinase is transactivated, phosphorylated by EGF receptor (Moulder *et al.*, 2001). HER2 expressing cells, such as the human breast tumor lines, are fast proliferating. Blocking EGF receptor phosphorylation with the orally active agent, ZD1839, ("Iressa") blocked phosphoryla-tion of HER2 in cells containing both tyrosine kinases, HER1 and HER2. This agent has about 200 times more specificity for the EGF receptor than for HER2 in tyrosine phosphorylation. It is suggested that agents targeting both HER1 and HER 2 should be used in breast tumors, which overexpress HER2 tyrosine kinase. ZD1839 is also active in mice xenografted with carcinoma cells (Ciardiello *et al.*, 2000). Another experimental drug, GW2016 was evaluated in a HN5 xenografted model (Mullin *et al.*, 2001). This compound is a specific inhibitor of EGF and erbB-2 tyrosine kinases GW2016, at a dose of 100 mg/kg twice a day for 21 days inhibited tumor growth by 101 + 20% without toxicity. The EGF phosphotyrosine level was greatly reduced in animals, indicating tyrosine kinase inhibition by this compound.

Cell differentiation agents

Many cancer cells may have increased sensitivity to growth factors and decreased sensitivity to differentiation signals. It has been thought that a sensible approach to cancer chemotherapy was to be development of agents which stop cell proliferation by inducing differ-entiation. One such agent, butyric acid, had some early success in the clinic (Novogradsky *et al.*, 1983). Butyric acid occurs in healthy people, in the colon. Mode of action studies revealed that hyperphosphorylation of the retinoblastoma protein, rb, is blocked by butyric acid (Buguet-Fagot *et al.*, 1996). Butyric acid also causes inhibition of cyclin-dependent kinase inhibitory protein mRNA, Wafl/CIP1 mRNA, in BP-A31 cells and cycline D1/PRAD1 protein, in carcinoma cells (Krupitza *et al.*, 1996). Pharmacokinetic studies in leukemia patients established that the half life of butyric acid is about 6 min and the clearance time is 1 h (Miller *et al.*, 1997). Because of this rapid clearance, derivatives with longer half life were developed. Pivaloyloxymethyl butyrate (PMbutyrate) and triglycerin tributyrate showed promis-ing results in cell culture and animal experiments (Raphaeli *et al.*, 1991; Nudelman *et al.*, 1992). Preclinical studies with baboons indicated that a schedule of 4 g/kg/day of continuous infusion of PMbutyrate for 2-3 weeks results in very little host-toxicity with definite efficacy (Blau *et al.*, 1993). One other product, phenylbutyrate, was shown to increase acetylation of histone H4 with the induction of $p21^{Waf1}$, independent of p53 modulation in TSU prostate cancer cell line (Tong *et al.*, 1996). In clinical trials, iv. infusion of phenyl-butyrate during a 120 h period, every 21 days, and up to 285 mg/kg/day, caused only minimal toxicity, and had some efficacy (Carducci *et al.*, 1996).

Another differentiating agent, all-trans retinoic acid, which is a metabolite of vitamin A, was found to modulate cell differentiation (Napoli, 1990; DeLuca, 1991). This active metabolite binds to the nuclear receptor RAR-alpha, beta and gamma. These receptors bind a complex of nuclear proteins and the retinoic acid in the promoter region causing changes in the transciption rates (de The et al., 1990). Another set of receptors, RXR alpha, beta and gamma, binds 9-cis retinoic acid, which is a metabolite of retinoic acid. All-trans retinoic acid was the most successful vitamin A derivative tested in the clinic, in acute promyelocytic leukemia (APL). It was found that patients that had successful treatment had a fusion protein of PML

and RAR-alpha (Rambaldi *et al.*, 1991). After this discovery, RT-PCR for the mRNA of this fused gene was used to screen for possible treatment efficacy with all-trans retinoic acid. In a trial with 22 patients the response rate was 63% with complete remission. The treatment schedule was 45 mg/m^2/day all-trans retinoic acid for three month (Muindi *et al.*, 1992). Unfortunately, a multiple type of resistance developed for this treatment in most patients. For skin cancers, such as xeroderma pigmentosum and squamous cell carcinoma, response rates of 63 and 47%, correspondingly, could be achieved with 0.5-2.0 mg/kg/day treatment with all-trans retinoic acid (Kraemer *et al.*, 1988; Lippman *et al.*, 1991).

Recently, all-trans retinoic acid was tried in combination with an approved drug for diabetes mellitus, pioglitazone. This drug is a ligand for peroxisome proliferator-activated receptor gamma. Together with all-trans retinoic acid, 10^{-5} mol, caused considerable apoptosis and inhibition of cell proliferation in breast and glioblastoma cancer cells. Singly these two drugs resulted in very little apoptosis and less inhibition of cell prolife-ration (Fritz *et al.*, 2001).

Telomerase Inhibitors

As mentioned in the introduction, telomerase enzyme plays a crucial role in malignant transformation of cells. This enzyme is responsible for maintaining telomeric DNA repeats during cell division, contributing to cancer cell proliferation (Bleckburn *et al.*, 1992; Harley *et al.*, 1994). Comparison of immortalized and somatic cells revealed that the former but not the latter, contain detectable amount of telomerase (Kim *et al.*, 1994). Also, telomerase can be detected in human cancer cells, such as gastric (Hiyama *et al.*, 1995) and neuro-blastoma (Hiyama *et al.*, 1995) cells, but not in normal cells taken from tissues adjacent to tumors. The above results suggested that telomerase activity is a reasonable target for specific cancer cell kill. Subsequently, it was shown that the telomerase enzyme functions on an intramolecular G-quadruplex structure of telomeric DNA. The prevention of such DNA-telomer structure formation was thought to be exploited for chemotherapeutic purposes. Two compounds were found to inhibit the required telomeric DNA structure, in vitro. One, 7-deaza-dATP was found to be an inhibitor of the telomerase activity (Fletcher *et al.*, 1996). The second, 3-azido-23-dideoxythymidine triphosphate was entered into clinical trials recently (Chen *et al.*, 1996).

Also, quinolone based ligands of G-quadruplex were found to impair telomerase activity and induce apop-tosis in twelve selected tumor lines. These experiments support the view that G-quadruplex DNA structures do exist in cells (Main *et al.*, 2001).

Farnesyl-group transferase inhibitors

Many functional proteins, enzymes achieve full activity when they are attached to cell membranes with a farnesyl group. For example, p21^{ras} protein is farnesy-lated after ligand binding to receptors, such as to EGF and T cell receptor, and its activity increases. Therefore, interruption of the farnesylation process of oncoproteins would slow cancer growth. This principle was demonstrated by the stable insertion of the antisense gene of the beta subunit of farnesyl transferase into carcinoma cells and resulting in inhibition of oncogenic signaling in vitro and in vivo (Sun *et al.*, 1996). Farnesyl trasferase activity can be inhibited by different types of compounds. One study, investigating an isoprenoid types of structures found that chain length and trans:trans conformation is important for specific inhibition of this enzyme in vitro as well as in vivo (Hohl *et al.*, 1996). Another study investigated a pentapep-tide, CBZ-L-his-tyr(OBenz)-ser-(Obenz)-trp-D-ala-NHZ, and found that it inhibited farnesyl transferase with an IC_{50} of 20 nM. A cell permeable derivative of this pentapeptide was a selective inhibitor of the enzyme in vitro and in vivo (Sebold-Leopold *et al.*, 1996).

The effect of farnesyl trasferases on tumor growth was demonstrated in in vivo experiments. For example, a mimetic of the carboxy terminus of K-ras 4B, inhibited the growth of human lung carcinoma with K-ras mutation and deletion of p53 gene xenografted into nude mice (Sun *et al.*, 1995). Similarly, excellent and selective results could be achieved with S,R-N-(L-(N-(2-amino-3-mercaptopropil)-L-tert-leucil)-1,2,3,4-tetrahydro-3-isoqui-nolinyl)-carboxyl-L-glutamine, a ras farnesyl transferase inhibitor, at a dose of 45 mg/kg, 2x/day in vitro and in vivo (Leftheris *et al.*, 1996).

It was found recently that application of selective farnesyl transferase inhibitors may mutate the ras oncoprotein. The mutated enzyme is resistant to its specific inhibitors because it gets activated by geranyl protein transferase I. Therefore, in some tumors both farnesyl- and geranyl-transferase inhibitors are necessary to block tumor growth (Bruser *et al.*, 2001). In addition to mutation, other proteins necessary for ras transformation, such as Rac I and RhoA are geranylgeranylated and induce malignant transformation (Sun *et al.*, 2001). With this in mind, the use of a peptidomimetic geranylgeranyl transferase inhibitor was administered to a nude mice bearing a mammary tumor. The in vivo effectiveness of this inhibitor proved that geranylgeranylated proteins, downstream of H-ras are required for mammary tumor genesis.

Several new farnesyl transferase inhibitors are in clinical evaluation, some in combination with other cell signal blockers. One example is R115777, a methyl quinolon, a competitive inhibitor of the CAAX peptide binding site of

the farnesyl transferase (Smith *et al.*, 2001). This compound was tried together with gemci-tabine in patients with solid tumor (Patnik *et al.*, 2001). Both compounds promote apoptotic pathways in cells. Results indicated that in 12 out of 16 patients the ratio of unfarnesylated proteins increased after treatment.

Another farnesyl transferase inhibitor SCH66336, is a tricyclic orally bioavailable drug, presently in clinical trials. During clinical trials, this compound was administered to non-small cell lung carcinoma patients, 100-150 mg/m^2 2 × per day together with paclitaxel. Notable partial responses were seen in all patients. The two drugs did not influence the pharmacokinetics of each other (Kim *et al.*, 2001). It was also found, in a separate study, that SCH 66336 prevents farnesylation of other than ras cellular proteins, increasing the effectiveness of this drug (Bishop *et al.*, 2001).

Immune system activators

Observations that tumor bearing humans are immunosuppressed led to the search of general immune stimulators to combat cancer. Recombinant cytokines were administered to cancer patients in many clinical trials. Also, different chemical compounds were tried in hopes of causing general immune stimulation. This discussion will deal only with compounds that induce cytokines resulting in immune stimulation. While this class of compounds with this mode of action are not exactly specific cancer cell signal blockers, they do suppress specifically the growth of cancer cells.

One compound with the potential to induce interferon-alpha (IFa) is bropirimine (Stringfellow *et al.*, 1980). It is a 5-halo-6-phenyl pyrimidinon nucleoside analog, and was shown to induce cellular immune response in animals and also to have antiviral activity (Lotzava *et al.*, 1983; Wierenga, 1985). Bropirimine was evaluated in renal cell carcinoma bearing nude mice. This type of cancer is resistant to chemotherapy and immunostimulation was thought to be a reasonable approach. Mice were xenografted with adenocarcinoma cells and then treated po. with different doses of bropirimine on day 1 or 6. The mean survival time of the treated animals increased to 38 days as compared to 28 days for the control animals (Fujioka *et al.*, 1995). The immune stimulation induced tumor suppression was related to NK and cytolytic T cell activity. This fact was shown by the finding that serum that eliminates NK and T cells, anti-asialo GM1 serum, reversed the effect of bropirimine. Also, it was shown that the IFa concentration was 9 times higher at 3 h after bropirimine administration in the serum of the treated animals as compared to the serum of the untreated animals. After showing clearly the immunostimulatory effect of this drug, clinical trials were started.

One early clinical trial evaluated 34 patients with cancer of the bladder (Sarosdy *et al.*, 1992). Dose escalation studies were using 20 to 70 mg/kg/day, 3 times/day, for 3 days per week for 12 weeks, resulting in an overall response rate of 31%. In the same study, patients with previous unsuccessful treatment with BCG also responded. Toxicity of the drug could be related to induction of high level IF, but was mild in nature.

An interesting observation was made with the EGF receptor tyrosine kinase inhibitor, ZD1839 (Budillon *et al.*, 2001). Namely, EGF receptor expressing melanoma, which resistant to MHC mediated killing, became sen-sitive to LAK cell cytotoxicity after treatment with this compound. Simultaneously downregulation of ERK1/ERK2 activity could also be demonstrated. This finding may open new possibilities for cancer immunetherapy.

Summary

This review was intended to highlight preclinical and clinical studies of chemotherapeutic agents with "specific" targets in cancer cells. No discussions were included of the many efforts using biological agents, such as cell mediated immunotherapy (dentric cells), the use of oncolytic viruses, or gene therapy.

We also recognize that there are drugs under study other than those mentioned in this review. For example, inhibitors, which block NF-kappaB function and prevent the initiation of proliferative cell signal, turned on by this nuclear factor. These inhibitors can enhance the effects of anti-cancer drugs. Potentiation of anti-cancer drugs also can be achieved by COX-2 inhibitors. Cell signaling through the COX-2 receptor results in prostaglandin E2 production and maintenance of cancer cell growth. An example of COX-2 inhibitor is nimesulide. This inhibitor was tried in lung, pancreas, prostate and colon cells because these cells usually express COX-2 receptors. Also, an autoregulatory cellular protein, MDM2, which forms an aduct with p53, blocks p53 functions by binding to its transcriptional transactivation domain on DNA. Compounds blocking this aduct formation can facilitate cell cycle arrest and apoptosis. At the present, we are not aware of significant clinical studies based on these and other promising preclinical approaches. Nevertheless, we do hope that this brief review may orient scientists and clinicians about recent developments in cancer chemotherapy.

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