

Cancer Treatment: The Critical Factors

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ABSTRACTS

Lovastatin augments sulindac-induced apoptosis in colon cancer cells and potentiates chemopreventive effects of sulindac.

Agarwal B, Rao CV, Bhendwal S, et al.

Gastroenterology. 1999 Oct; 117(4):838-47.

BACKGROUND & AIMS: 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (HRI) were found incidentally to reduce new cases of colon cancer in 2 large clinical trials evaluating coronary events, although most patients in both treatment and control group were taking nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are associated with reduced colon cancer incidence, predominantly by increasing apoptosis. We showed previously that lovastatin induces apoptosis in colon cancer cells. In the present study we evaluated the potential of combining lovastatin with sulindac for colon cancer chemoprevention. **RESULTS:** Lovastatin, 10-30 micromol/L, augmented sulindac-induced apoptosis up to 5-fold in 3 colon cancer cell lines. This was prevented by mevalonate (100 micromol/L) or geranylgeranylpyrophosphate (10 micromol/L) but not farnesylpyrophosphate (100 micromol/L), suggesting inhibition of geranylgeranylation of target protein(s) as the predominant mechanism. In an azoxymethane rat model of chemical-induced carcinogenesis, the total number of colonic aberrant crypt foci per animal (control, 161 +/- 11) and the number of foci with 4+ crypts (control, 40 +/- 4.5) decreased to 142 +/- 14 (NS) and 43 +/- 2.9 (NS), respectively, with 50 ppm lovastatin alone; to 137 +/- 5.4 (P = 0.053) and 36 +/- 2.1 (NS) with 80 ppm sulindac alone; and to 116 +/- 8.1 (P = 0.004) and 28 +/- 3.4 (P = 0.02) when 50 ppm lovastatin and 80 ppm sulindac were combined. **CONCLUSIONS:** Addition of an HRI such as lovastatin may augment chemopreventive effects of NSAIDs or/and may allow lower, less toxic doses of these drugs to be used

Ras oncogenes: ras oncogenes in human cancer: a review 1990.

Anon.

Cancer Res. 1990; 50(4):1352.

Mammary carcinomas induced in human c-Ha-ras proto-oncogene transgenic rats are estrogen-independent, but responsive to d-limonene treatment.

Asamoto M, Ota T, Toriyama-Baba H, et al.

Jpn J Cancer Res. 2002 Jan; 93(1):32-5.

We have previously shown that transgenic rats carrying three copies of the human c-Ha-ras proto-oncogene (Hras128) are highly susceptible to N-methyl-N-nitrosourea (MNU) mammary carcinogenesis. All transgenic rats treated with 50 mg / kg MNU, i.v. at 50 days of age, were found to rapidly develop multiple, large mammary carcinomas within as short a period as 8 weeks. In the present study, the effects of ovariectomy and treatment with d-limonene, known to inhibit mammary carcinogenesis in non-transgenic female rats, were investigated in Hras128 animals treated with MNU to clarify the role of the human c-Ha-ras proto-oncogene and to characterize the induced mammary carcinomas. Although ovariectomy completely inhibited development of mammary carcinomas in their wild-type counterparts, it did not affect either the incidence or the multiplicity of the mammary carcinomas in the Hras128 rats. On the other hand, treatment with d-limonene, an inhibitor of ras protein isoprenylation, inhibited the breast tumor development. These results indicate that aberrant c-Ha-ras gene expression is involved in ovarian hormone-independent growth and c-Ha-ras protein isoprenylation plays an important role in mammary carcinogenesis

Mutations in ras genes in myelocytic leukemias and myelodysplastic syndromes.

Bartram CR.

Blood Cells. 1988; 14(2-3):533-8.

Acute myelocytic leukemias (AML) are characterized by a remarkably high incidence (approximately 30%) of point mutations affecting codons 12, 13, or 61 within ras genes. A predominant involvement of N-ras sequences has been established. Neither Philadelphia chromosome-positive chronic myelocytic leukemia nor other chronic myeloproliferative disorders show a similar frequency. However, a proportion of myelodysplastic syndromes, namely, the chronic myelomonocytic subtype (CMML) also show this molecular feature. The following is a brief discussion of the possible biologic and clinical implications of these observations

Farnesyl transferase inhibitors.

Bland J.

2001;October 17-21, 2001;

Aseptic meningitis associated with rofecoxib.

Bonnel RA, Villalba ML, Karwoski CB, et al.

Arch Intern Med. 2002 Mar 25; 162(6):713-5.

Rofecoxib is a nonsteroidal anti-inflammatory drug that is reported to act by selectively inhibiting cyclooxygenase-2. A review and analysis of reports sent to the Spontaneous Reporting System of the Food and Drug Administration, Rockville, Md, suggest that aseptic meningitis is associated with rofecoxib use. To our knowledge, there have been no published reports of aseptic meningitis occurring in association with rofecoxib use to date. We report 5 serious cases of aseptic meningitis associated with rofecoxib use

Aspirin linked to aid in colon cancer fight.

Brody JE.

New York Times. 1991; 141(48, 812):A12.

[Pulmonary embolism of paraneoplastic origin].

Cafagna D, Ponte E.

Minerva Med. 1997 Dec; 88(12):523-30.

Thromboembolic disease (TE) is an important cause of in-hospital morbidity and mortality. The relationship between cancer and abnormalities of blood coagulation has been recognized for well over a century. Deep venous thrombosis (DVT) of the lower extremities is the most common cause of thromboembolic disease, but pulmonary embolism, upper extremity vein thrombosis, disseminated intravascular coagulation, and other, more unusual, clinical events, may occur. Unexplained TE may serve as a marker for the presence of a hidden tumor. The frequency of pulmonary embolism (PE) among patients with a malignant neoplasm at necropsy is highly increased in the elderly patients. Among subjects with a malignant neoplasm, patients with pancreatic and gastric cancer (mucin-secreting adenocarcinomas), cancer of the large bowel and women with ovarian cancer had the highest frequency of PE. Old age, female sex, gastrointestinal and ovarian cancers must be considered as a significant risk factor for PE. The potentially responsible mechanisms for the thrombotic events, clinical manifestations, diagnostic implications and aspects of treatment of TE in malignant disease are discussed

Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review.

Caro JJ, Salas M, Ward A, et al.

Cancer. 2001 Jun 15; 91(12):2214-21.

BACKGROUND: Anemia is common in cancer patients, although the prevalence is influenced both by the type of malignancy and the choice of treatment. Individual studies have compared the survival of patients with and without anemia and have shown reduced survival times in patients with various malignancies, including carcinoma of the lung, cervix, head and neck, prostate, lymphoma, and multiple myeloma. The objective of this study was to systematically review, to summarize, and to obtain an overall estimate of the effect of anemia on survival in patients with malignant disease. **METHODS:** A comprehensive literature review was carried out using the MEDLINE data base and reviewing the reference lists from published studies. Two hundred

papers were identified. Of these, 60 papers that reported the survival of cancer patients according to either hemoglobin levels or the presence of anemia were included. Among these papers, 25% related to patients with lung carcinoma, 17% related to patients with head and neck carcinoma, 12% related to patients with multiple myeloma, 10% related to patients with prostate carcinoma, 8% related to patients with cervicouterine carcinoma, 7% related to patients with leukemia, 5% related to patients with lymphoma, and 16% related to patients with other types of malignancies. RESULTS: The relative risk of death increased by 19% (95% confidence interval, 10-29%) in anemic patients with lung carcinoma, by 75% (37-123%) in anemic patients with head and neck carcinoma, by 47% (21-78%) in anemic patients with prostate carcinoma, and by 67% (30-113%) in anemic patients with lymphoma. The overall estimate increase in risk was 65% (54-77%). CONCLUSIONS: Anemia is associated with shorter survival times for patients with lung carcinoma, cervicouterine carcinoma, head and neck carcinoma, prostate carcinoma, lymphoma, and multiple myeloma

Mechanisms of anaemia in patients with malignancy: implications for the clinical use of recombinant human erythropoietin.

Cazzola M.

Med Oncol. 2000 Nov; 17 Suppl 1:S11-S16.

Anaemia is a frequent finding in cancer and may be due to different causes. In untreated subjects, the most common type is the so-called anaemia of chronic disease, a condition characterised by excessive release of cytokines such as interleukin-1 and tumour necrosis factor. These peptides both inhibit erythroid marrow proliferation and blunt the normal exponential relationship between haematocrit and serum erythropoietin. Chemotherapy may cause or worsen anaemia in cancer patients. Cisplatin appears to be peculiar in that this drug can blunt erythropoietin production and cause prolonged anaemia. Controlled studies have demonstrated that recombinant human erythropoietin (rHuEPO) can ameliorate anaemia in patients with malignancy and prevent chemotherapy-induced anaemia. However, improvement of anaemia following rHuEPO treatment is seen in only a portion of cancer patients, and significant improvements of quality of life cannot be demonstrated in all responsive patients. Therefore, an important issue remains whom to treat

A randomized trial of anticoagulation with warfarin and of alternating chemotherapy in extensive small-cell lung cancer by the Cancer and Leukemia Group B.

Chahinian AP, Propert KJ, Ware JH, et al.

J Clin Oncol. 1989 Aug; 7(8):993-1002.

The Cancer and Leukemia Group B (CALGB) conducted a prospective randomized trial to evaluate the role of warfarin and alternating chemotherapy in extensive small-cell lung cancer (SCCL). After stratification for sex and performance status, patients were randomly assigned to receive chemotherapy with methotrexate, doxorubicin (Adriamycin; Adria Laboratories, Columbus, OH), cyclophosphamide, and lomustine (CCNU) (MACC), or MACC plus warfarin (MACC + W), or mitomycin, etoposide, cisplatin, and hexamethylmelamine alternating with MACC (MEPH/MACC). Warfarin was given continuously to maintain a prothrombin time of one and one half to twice the control values. A total of 328 patients were enrolled, and 294 were evaluable. There was a statistically significant advantage in objective response rates (complete [CR] and partial responses [PR], respectively) for MACC + W (17% and 50%) as compared with MACC alone (8% and 43%) or MEPH/MACC (10% and 38%) ($P = .012$). Both failure-free survival ($P = .054$ Wilcoxon test) and overall survival ($P = .098$ Wilcoxon test) were higher on MACC + W (median, 6.6 months and 9.3 months, respectively), as compared with MACC (5.0 months and 7.9 months) and MEPH/MACC (5.0 months and 7.9 months). Toxicity was comparable among the three arms, except for increased hemorrhagic events on MACC + W, which were life-threatening in four patients (4%), and lethal in two others (2%). These data support the role of warfarin in the treatment of SCCL, but do not establish its mechanism of action. Warfarin deserves further studies in SCCL, particularly in patients with limited disease

Inhibition of activator protein 1 activity and cell growth by purified green tea and black tea polyphenols in H-ras-transformed cells: structure-activity relationship and mechanisms involved.

Chung JY, Huang C, Meng X, et al.

Cancer Res. 1999 Sep 15; 59(18):4610-7.

ras gene mutation, which perpetually turns on the growth signal transduction pathway, occurs frequently in many cancer types. The mouse epidermal JB6 cell line has been transfected with a mutant H-ras gene to mimic carcinogenesis in vitro. These transformed cells (30.7b Ras 12) are able to grow in soft agar, exhibiting anchorage independence and high endogenous activator protein 1 (AP-1) activity, which can be detected by a stable AP-1 luciferase reporter. The present study investigated the ability of different pure green and black tea polyphenols to inhibit this ras signaling pathway. The major green tea polyphenols (catechins), (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin, (-)-epicatechin-3-gallate, (-)-epicatechin, and their

epimers, and black tea polyphenols, theaflavin-3-gallate, theaflavin-3'-gallate, and theaflavin-3,3'-digallate (TFdiG), were compared with respect to their ability to inhibit the growth of 30.7b Ras 12 cells and AP-1 activity. All of the tea polyphenols except (-)-epicatechin showed strong inhibition of cell growth and AP-1 activity. Among the catechins, both the galloyl structure on the B ring and the gallate moiety contributed to the growth inhibition and AP-1 activity; the galloyl structure appeared to have a stronger effect on the inhibitory action than the gallate moiety. The epimers of the catechins showed similar inhibitory effects on AP-1 activity. The addition of catalase to the incubation of the cells with EGCG or TFdiG did not prevent the inhibitory effect on AP-1 activity, suggesting that H₂O₂ does not play a significant role in the inhibition by tea polyphenols. Both EGCG and TFdiG inhibited the phosphorylation of p44/42 (extracellular signal-regulated kinase 1 and 2) and c-jun without affecting the levels of phosphorylated-c-jun-NH₂-terminal kinase. TFdiG inhibited the phosphorylation of p38, but EGCG did not. EGCG lowered the level of c-jun, whereas TFdiG decreased the level of fra-1. These results suggest that tea polyphenols inhibited AP-1 activity and the mitogen-activated protein kinase pathway, which contributed to the growth inhibition; however, different mechanisms may be involved in the inhibition by catechins and theaflavins

n-6 and n-3 polyunsaturated fatty acids differentially modulate oncogenic Ras activation in colonocytes.

Collett ED, Davidson LA, Fan YY, et al.

Am J Physiol Cell Physiol. 2001 May; 280(5):C1066-C1075.

Ras proteins are critical regulators of cell function, including growth, differentiation, and apoptosis, with membrane localization of the protein being a prerequisite for malignant transformation. We have recently demonstrated that feeding fish oil, compared with corn oil, decreases colonic Ras membrane localization and reduces tumor formation in rats injected with a colon carcinogen. Because the biological activity of Ras is regulated by posttranslational lipid attachment and its interaction with stimulatory lipids, we investigated whether docosahexaenoic acid (DHA), found in fish oil, compared with linoleic acid (LA), found in corn oil, alters Ras posttranslational processing, activation, and effector protein function in young adult mouse colon cells overexpressing H-ras (YAMC-ras). We show here that the major n-3 polyunsaturated fatty acid (PUFA) constituent of fish oil, DHA, compared with LA (an n-6 PUFA), reduces Ras localization to the plasma membrane without affecting posttranslational lipidation and lowers GTP binding and downstream p42/44(ERK)-dependent signaling. In view of the central role of oncogenic Ras in the development of colon cancer, the finding that n-3 and n-6 PUFA differentially modulate Ras activation may partly explain why dietary fish oil protects against colon cancer development

[Vinorelbine in the treatment of breast cancer: current status and prospectives for the future].

Conti F, Vici P.

Clin Ter. 1998 Jan; 149(921):61-74.

PURPOSE: To evaluate efficacy and tolerability of vinorelbine in breast cancer. **DESIGN:** A review of most significant and recent clinical trials was performed. **RESULTS:** Vinorelbine as single agent showed 44% and 17.36% of response as 1st and 2nd line treatment, respectively. When combined with other agents, these figures were the following: cisplatin, 73%-75% and 43-64%; mitomycin C, up to 92% and 33%-69%; 5-fluorouracil, 33%-64% and 22%-55%; ifosfamide, 57% and 28%; taxol, 78% and 54%; taxotere, up to 80%; mitoxantrone, 44%-68% and 31%-40%; doxorubicin, 57%-82% and 30%-33%; epirubicin, 22%-78% and 33%. Vinorelbine-epirubicin combination appears to be very active in neoadjuvant setting, with up to 92% response rates. **CONCLUSIONS:** Vinorelbine activity is significant and similar to that of the most active antineoplastic drugs in breast cancer. The most promising combinations appear to be with anthracyclines, taxanes or mitomycin C, even in heavily pretreated patients. Some aspects, such as optimal dose and scheduling and the inclusion in adjuvant programs or in new combination regimens remain to be defined

Improved cancer mortality with low-molecular-weight heparin treatment: a review of the evidence.

Cosgrove RH, Zacharski LR, Racine E, et al.

Semin Thromb Hemost. 2002 Feb; 28(1):79-87.

Work with low-molecular-weight heparins (LMWHs) continues to provide suggestions for survival advantages among patients with cancer diagnoses. Momentum is building in support of this theory through reports, the vast majority of which are derived from secondary analyses of clinical trials on the treatment of thromboembolism. The data retrieved from such studies that compare unfractionated heparin (UFH) with LMWH indicate that LMWH is equally beneficial if not more beneficial to cancer patients in terms of survival. In retrospective analysis, this improved life expectancy is not considered a result of reduced complications from thromboembolism. Thus, theories of antitumor effects of LMWH have developed, supported by evidence that most of the survival benefits are during long-term comparisons. Reports describing the effects of heparin in the setting of cancer have existed for over a half-century, although specific mechanisms for the marginal results seen thus far have yet to surface. Proposals for the

most likely targets of the effective heparins include enzyme interaction, cellular growth modifications, and antiangiogenesis

Vinorelbine + mitomycin C as second-line treatment of metastatic breast cancer: a two-stage phase 2 study.

De Placido S, Lauria R, Perrone F, et al.

Oncology. 2000; 58(1):8-14.

Second-line treatment of patients with metastatic breast cancer resistant to anthracyclines is an important clinical issue. The aim of the present two-stage phase II study was to evaluate activity and toxicity of vinorelbine + mitomycin C (VM) in such patients. Fifty-five patients were entered and received vinorelbine 30 mg/m² on days 1 and 8 + mitomycin C 10 mg/m² on day 1, every 4 weeks, up to 9 cycles. Two complete and 23 partial responses were observed for an overall response rate of 45.4% (95% CI 32.0-59.4). Median survival was 13 months and probability of surviving after a 1-year follow-up was 58%. Toxicity was never life-threatening, but G-CSF was used in 45% of cycles to contrast neutropenia that was the most frequent side effect. These results are consistent with previous studies and strongly support VM being considered among the optimal polychemotherapy regimens for second-line treatment of metastatic breast cancer in clinical practice; for clinical research aims, VM should be used as control arm for randomized trials evaluating the activity of new drugs against breast cancer

Low hemoglobin is associated with increased serum levels of vascular endothelial growth factor (VEGF) in cancer patients. Does anemia stimulate angiogenesis?

Dunst J, Pigorsch S, Hansgen G, et al.

Strahlenther Onkol. 1999 Mar; 175(3):93-6.

BACKGROUND: Vascular endothelial growth factor (VEGF) is an endothelial cell specific mitogen with strong angiogenic activity. Expression of VEGF may therefore be an indicator for the angiogenic potential and biological aggressiveness of a tumor. Recently, measurement of the VEGF-protein in sera has become available. We report results of serum-VEGF in an unselected group of patients with cancer with special emphasis on a possible role of anemia. **PATIENTS AND METHODS:** Between August 1997 and January 1998, serum-levels of VEGF were determined in a total number of 54 consecutive patients with previously untreated, non-metastatic carcinomas at the Department of Radiotherapy at the Martin-Luther University Halle-Wittenberg. The age ranged from 35 through 89 years with a median age of 67 years. All patients had locoregional confined disease without evidence of hematogenous metastases. Tumor sites were gynecological cancers in 22, head and neck in 14, gastrointestinal in 13, lung in 4 and prostate in 1 case. Forty-four patients had squamous carcinomas and 10 adenocarcinomas. Prior to treatment, routine laboratory work-up was done including measurement of serum-vascular endothelial growth factor (VEGF). The pretreatment hemoglobin ranged from 8.9 through 15.6 g/dl with a median of 13 g/dl. VEGF was measured with a quantitative sandwich enzyme immunoassay technique. **RESULTS:** The serum levels of VEGF in 40 patients with benign diseases ranged from 57 through 891 pg/ml with a mean of 267 +/- 170 pg/ml. In the investigated 54 cancer patients, VEGF ranged from 62 through 2,609 pg/ml with a mean of 614 +/- 551 pg/ml. Age, UICC/FIGO-stage, T- or N-category, primary tumor site, grade and histologic type had no significant impact on VEGF-serum levels. There was, however, an association between hemoglobin level and serum-VEGF with an increased mean serum-VEGF in 26 patients with a low hemoglobin (< 13 g/dl) as compared to 28 patients with a hemoglobin > 13 g/dl (805 +/- 656 vs 438 +/- 360, p = 0.016, 2-sided t-test). **CONCLUSIONS:** With regard to the recently established correlation between anemia and intratumoral hypoxia, the increased serum-VEGF levels in patients with low hemoglobin may be explained via hypoxia-induced VEGF secretion. This would suggest that anemia may stimulate angiogenesis via hypoxia. The hypothesis, however, requires further investigation and might have important therapeutical impact

Ras interference as cancer therapy.

Duursma AM, Agami R.

Semin Cancer Biol. 2003 Aug; 13(4):267-73.

Activating point mutations of the small GTPase Ras are present in about 30% of all human tumors. Constitutively active Ras induces growth factor independent cell proliferation and cell survival. Oncogenic Ras appears to be essential for tumor progression and maintenance. Several therapeutic agents have been developed to inhibit Ras, such as FTIs and antisense oligonucleotides. A new tool for blocking oncogenes in cancer cells has emerged with the discovery that RNA interference can specifically silence expression of endogenous human genes. The therapeutic potential of a RNAi-mediating vector was recently demonstrated by the stable suppression of oncogenic K-Ras in tumor cells

Transient reversion of ras oncogene-induced cell transformation by antibodies specific for amino acid 12 of ras protein.

Feramisco JR, Clark R, Wong G, et al.

Nature. 1985 Apr 18; 314(6012):639-42.

The proteins encoded by the ras oncogene are thought to trigger expression of the transformed phenotype in some types of cancer cells. In human cells, the ras protein family consists of several members including normal (proto-oncogene) and mutant (oncogene) forms. In general, the proto-oncogene forms are thought to be involved in the normal growth control of cells, while the mutant forms (which apparently result from somatic mutation of the normal ras genes) appear to be responsible, in part, for the loss of normal growth control. On microinjection into living normal cells, the purified ras oncogene protein (p21) induces a characteristic loss of growth control in cells within several hours. The mutant forms of the different ras proteins typically contain a single amino-acid change, usually at position 12 or less frequently at position 61. Here we report that microinjection of antibodies specific for amino acid 12 of the oncogenic v-Ki-ras protein into cells transformed by this protein causes a transient reversion of the cells to a normal phenotype. The fact that this antibody inhibits binding of GTP to the v-Ki-ras protein supports the notion that GTP binding is essential to the transforming function of this oncogene product

Control of angiogenesis by heparin and other sulfated polysaccharides.

Folkman J, Shing Y.

Adv Exp Med Biol. 1992; 313:355-64.

Heparin and its related polysaccharides are revealed to have important new functions as regulators of blood vessel growth and regression. This regulatory activity may be explained in part by at least five mechanisms in which heparin and heparan sulfate interact with peptide growth factors: (1) Heparin and heparan sulfate have a high affinity for angiogenic growth factors such as the fibroblast growth factors and VEGF, as well as for angiogenic inhibitors such as thrombospondin and platelet factor 4. (2) Heparin and its related polysaccharides stabilize bFGF and other growth factors. (3) FGFs and thrombospondin are stored in the extracellular matrix bound to heparan sulfate; fragments of heparin or heparan sulfate may act as natural chaperones to shuttle bFGF or other growth factors to different cellular compartments. (5) Heparin-like low-affinity receptors on the surface of endothelial cells (and other cells), prepare FGFs for binding to their specific high affinity receptors; and (6) Heparin and its related polysaccharides potentiate angiostatic steroids. It is likely that future investigations will uncover even more fundamental regulatory roles for heparin as well as for other polysaccharides in the normal function of growth factors, especially in the complex process of angiogenesis

The role of angiogenesis in tumor growth.

Folkman J.

Semin Cancer Biol. 1992 Apr; 3(2):65-71.

Experimental and clinical evidence is here assembled in support of the concept that the development of a solid tumor progresses from a prevascular phase to a vascular phase. The prevascular tumor does not induce angiogenesis, is limited in size, and rarely metastasizes. The vascularized tumor induces host microvessels to undergo angiogenesis, has the potential to rapidly expand its cell population, and has a propensity to metastasize. Thus, angiogenesis is necessary but not sufficient for tumor growth and metastasis. Neovascularization of a tumor requires that a critical number of its cells have switched to the angiogenic phenotype. The mechanisms by which tumor cells become angiogenic, subjects of current study, are reviewed here. At least two general categories are recognized: (i) angiogenic activity arises from the tumor cell itself in the form of the release of angiogenic molecules such as basic fibroblast growth factor; (ii) angiogenic activity arises from host cells recruited by the tumor (e.g. macrophages), or is mobilized from the extracellular matrix, or requires concomitant loss of physiological inhibition of endothelial cell proliferation. Accumulating evidence indicates that for most tumors, the switch to the angiogenic phenotype depends upon the outcome of a balance between angiogenic stimulators and angiogenic inhibitors, both of which may be produced by tumor cells and perhaps by certain host cells

A phase I-II study on a gemcitabine-cyclophosphamide-fluorouracil/folinic acid triplet combination in anthracycline- and taxane-refractory breast cancer patients.

Frasci G, D'Aiuto G, Comella P, et al.

Oncology. 2002; 62(1):25-32.

PURPOSE: To define the cyclophosphamide (CTX) maximal tolerated dose when combined with fixed doses of gemcitabine, fluorouracil (5-FU) and folinic acid (leucovorin, LFA) in metastatic breast cancer patients pretreated with anthracyclines and

taxanes. METHODS: Metastatic breast cancer patients aged \leq 75 years, with ECOG performance status 0-2, were eligible, provided that they had received previous anthracycline- and taxane-based chemotherapy for the advanced disease. Chemotherapy consisted of gemcitabine 1,000 mg/m², 5-FU 425 mg/m², LFA 100 mg/m² and escalating doses of CTX, starting from 500 mg/m², on days 1 and 8 every 3 weeks. The dose escalation was stopped if dose-limiting toxicity (DLT) occurred in $>$ 33% of patients of a given cohort. After the definition of DLT, a further escalation with the addition of granulocyte colony-stimulating factor (G-CSF; on days 3-5 and 10-12) was planned. RESULTS: Since March 1999, 69 patients have entered this trial through seven different cohorts. The dose escalation was stopped at the CTX dose of 600 mg/m² since 3/6 patients showed DLT. A further dose escalation was attempted in the presence of G-CSF support. A CTX dose of 800 mg/m² proved to be safe and was chosen for the phase II. A total of 33 patients were treated at this dose level. The treatment was fairly well tolerated, grade 3-4 neutropenia and thrombocytopenia occurring in 38 and 16% of patients, respectively. No cases of sepsis or bleeding were registered. Four patients required a packed red blood cell transfusion. Severe nonhematologic toxicity was also uncommon, occurring in 10 patients. Three complete and 24 partial responses were recorded for an overall response rate of 38% (95% CI = 26-50). Two complete and 12 partial responses were recorded in the 33 patients treated in the phase II for an overall response rate (ORR) of 42% (95% CI = 25-61). CONCLUSIONS: The gemcitabine-CTX-5-FU/LFA combination is a well-tolerated treatment for poor-prognosis breast cancer patients with previous exposure to anthracyclines and taxanes. With the addition of G-CSF, a cumulative CTX dose of 1,600 mg/m² can be safely delivered every 3 weeks. The evidence of an ORR approaching 40% is very promising and justifies further evaluations in this subset of patients

The contributions of cyclooxygenase-2 to tumor angiogenesis.

Gately S.

Cancer Metastasis Rev. 2000; 19(1-2):19-27.

Cyclooxygenase-2 (COX-2) is an immediate early response gene that can be induced by a variety of tumor promoters, cytokines, growth factors and hypoxia. COX-2 overexpression is linked to all stages of carcinogenesis with the enzyme localized to the neoplastic cells, microvascular endothelial cells, and stromal fibroblasts. The contributions of COX-2 in tumor angiogenesis include: (a) the increased expression of the proangiogenic growth factor VEGF; (b) the production of the eicosanoid products thromboxane A₂, PGE₂ and PGI₂ that can directly stimulate endothelial cell migration and growth factor-induced angiogenesis; and potentially, (c) the inhibition of endothelial cell apoptosis by stimulation of Bcl-2 or Akt activation. Selective pharmacological inhibitors of COX-2 as angiosuppressive agents could have therapeutic benefit in the treatment of neoplastic disease from prevention through treatment of advanced metastatic disease. These agents are safe and well tolerated and can be added to chemotherapy and radiation therapy where angiogenesis inhibitors appear to provide at least additive therapeutic benefit

Farnesyltransferase inhibitors and anti-Ras therapy.

Gibbs JB, Kohl NE, Koblan KS, et al.

Breast Cancer Res Treat. 1996; 38(1):75-83.

The oncoprotein encoded by mutant ras genes is initially synthesized as a cytoplasmic precursor which requires posttranslational processing to attain biological activity; farnesylation of the cysteine residue present in the CaaX motif located at the carboxy-terminus of all Ras proteins is the critical modification. Once farnesylated and further modified, the mature Ras protein is inserted into the cell's plasma membrane where it participates in the signal transduction pathways that control cell growth and differentiation. The farnesylation reaction that modifies Ras and other cellular proteins having an appropriate CaaX motif is catalyzed by a housekeeping enzyme termed farnesyl-protein transferase (FPTase). Inhibitors of this enzyme have been prepared by several laboratories in an effort to identify compounds that would block Ras-induced cell transformation and thereby function as Ras-specific anticancer agents. A variety of natural products and synthetic organic compounds were found to block farnesylation of Ras proteins in vitro. Some of these compounds exhibit antiproliferative activity in cell culture, block the morphological alterations associated with Ras-transformation, and can block the growth of Ras-transformed cell lines in tumor colony-forming assays. By contrast, these compounds do not affect the growth or morphology of cells transformed by the Raf or Mos oncoproteins, which do not require farnesylation to achieve biological activity. The efficacy and lack of toxicity observed with FPTase inhibitors in an animal tumor model suggest that specific FPTase inhibitors may be useful for the treatment of some types of cancer

Vinorelbine (Navelbine) in the treatment of non-small-cell lung cancer: studies with single-agent therapy and in combination with cisplatin.

Gralla R, Harper P, Johnson S, et al.

Ann Oncol. 1999; 10 Suppl 5:S41-S45.

Initial studies of vinorelbine (Navelbine) given as a single agent to patients with operable non-small-cell lung cancer (NSCLC) showed that overall response rates of the order of 30% could be obtained with a schedule of 30 mg/m² given weekly. Although such high levels of response have seldom been obtained when vinorelbine is given alone in one arm of a comparative study, the level of activity is clearly worthwhile and represents a significant improvement over supportive care. Combination therapy with cisplatin has been highly successful, establishing Vinorelbine as a safe well-tolerated agent which provides considerable activity, and experience from large phase III studies suggests that the combination of vinorelbine and cisplatin could represent a reference schedule against which other therapy should be compared

Vinorelbine (navelbine) in the treatment of non-small-cell lung cancer: recent developments in combination chemotherapy and radiotherapy.

Gralla R, Harper P, Johnson S, et al.

Ann Oncol. 1999; 10 Suppl 5:S47-S51.

The investigation of the activity of vinorelbine in non-small-cell lung cancer (NSCLC) has continued beyond the initial studies which established its single agent activity and defined the combination of vinorelbine and cisplatin as one of the standard treatments for inoperable NSCLC. Alternative partners to cisplatin have been evaluated in combination therapy with vinorelbine with promising results emerging from combinations with carboplatin, ifosfamide, mitomycin C and gemcitabine. Three drug combinations such as vinorelbine, cisplatin and ifosfamide can clearly produce high response rates in patients with good performance status at the time of treatment. The ability of vinorelbine to contribute to disease reduction either alone or in combination with other cytotoxic drugs has made it possible to consider its use in neo-adjuvant therapy, while the synergistic action of vinorelbine with radiotherapy has encouraged the use of sequential or concomitant chemoradiotherapy producing high response rates after completion of both modalities. The possible role of post-operative adjuvant treatment with Vinorelbine either alone or in combination with cisplatin is being assessed in a prospective trial

Phase II evaluation of 3-day topotecan with cyclophosphamide in the treatment of recurrent ovarian cancer.

Hanjani P, Nolte S, Shahin MS.

Gynecol Oncol. 2002 May; 85(2):278-84.

OBJECTIVE: The aim of this trial was to investigate the toxicity and efficacy of a 3-day topotecan administration schedule in combination with cyclophosphamide in the management of recurrent ovarian cancer. **METHODS:** Patients with recurrent measurable ovarian cancer who had up to two prior chemotherapy regimens for the management of their disease participating in this phase II trial were to receive topotecan at a dose of 1.25 mg/m²/day x 3 days in combination with cyclophosphamide at 600 mg/m² on Day 1 every 21 days. Dose escalation and reductions were permitted. **RESULTS:** A total of 36 patients (median age = 65; range 37-84) were treated with this combination regimen. Seventeen were platinum-sensitive and 19 were platinum-resistant. A total of 169 cycles of chemotherapy was administered (median = 4; range 1-10). Major toxicity included grade 4 neutropenia (68.6%), neutropenic fever (7.1%), grade 3 thrombocytopenia (18.3%), and requirement for blood transfusion (19.5%). Dose escalation was possible in 3 (8.3%), and dose reduction was required in 14 (38.9%) patients. Overall response rate was 25 and 44.5% stable disease. Median progression-free interval and overall survival was 5.4 and 23.5 months, respectively, independent of platinum sensitivity. **CONCLUSION:** The 3-day topotecan schedule in combination with cyclophosphamide appears to have good activity in recurrent ovarian cancer regardless of platinum sensitivity. Neutropenia was the only severe toxicity and was less prevalent than other reported trials of topotecan. This tolerable regimen offers patients more convenience and appears to have moderate activity

ICON 2 and ICON 3 data in previously untreated ovarian cancer: results to date.

Harper P.

Semin Oncol. 1997 Oct; 24(5 Suppl 15):S15.

The second International Collaborative Ovarian Neoplasm study (ICON 2), was a large, international randomized study of cyclophosphamide/doxorubicin/cisplatin (CAP) versus single-agent carboplatin in patients with previously untreated ovarian cancer. Patients in the CAP arm received 500 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, and 50 mg/m² cisplatin. Carboplatin was dosed to an area under the concentration-time curve of 5. Chemotherapy was given every 3 weeks for a total of 6 months for each regimen. Results of a 1995 interim analysis in 1,377 patients showed that overall, the total dose received in the CAP group was greater than 75% of the planned dose, with 75% of patients receiving greater than 87%, greater than 80%, and greater than 83% of the planned doses of cisplatin, doxorubicin, and cyclophosphamide, respectively. Of carboplatin patients, 75% received greater than 1,450 mg/m² (of a median planned dose of 1,800 mg/m²). There were significant differences

in grades 3/4 toxicity between the two arms: leukopenia occurred in 34% of CAP patients versus 10% of carboplatin patients, alopecia in 70% versus 3%, nausea and vomiting in 21% versus 9%, and mucositis in 21% versus 0%, respectively. However, thrombocytopenia was more frequent in the carboplatin group (16% v 7%). At the 1996 analysis, 1,526 patients had been entered, 1,498 had been randomized, and 740 had progressed or died. The interim conclusions were that although the more toxic CAP regimen may improve progression-free survival by a small amount, there was no evidence of any survival benefits or difference within the subgroups. Given that a sufficient number of patients had been accrued to ICON 2 and that starting accrual for ICON 3 markedly slowed accrual to ICON 2, the trial was closed. The full analysis of ICON 2 should be available in the summer of 1997. ICON 3 was designed to consider the role of paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) in previously untreated ovarian cancer. Patients received paclitaxel at a dose of 175 mg/m² (3-hour infusion) in combination with carboplatin dosed to an area under the concentration-time curve of 5 (based on chromium ethylenediamine tetraacetic acid) or 6 (based on calculated creatinine clearance). The control arm was either CAP or carboplatin. Patients were randomized 2:1 in favor of the control arm. In all, 1,070 patients have been entered to date. At the first planned interim analysis, in April 1996 in 434 patients, it was too early to provide efficacy data. The plan was to continue accruing to the trial to a maximum of 2,000 patients, with review in mid-1997, when the events for analysis will be virtually doubled and the data can be interpreted in light of the results of the Intergroup study (European Organization for Research and Treatment of Cancer, the National Cancer Institute of Canada, and the Scottish study) and Gynecologic Oncology Group trial 132

Melatonin prevents oxidative stress resulting from iron and erythropoietin administration.

Herrera J, Nava M, Romero F, et al.

Am J Kidney Dis. 2001 Apr; 37(4):750-7.

Intravenous iron (Fe) and recombinant human erythropoietin (rHuEPO) are routine treatments in the management of anemia in patients with chronic renal failure. We investigated the oxidative stress acutely induced by these therapies and whether pretreatment with oral melatonin (MEL) would have a beneficial effect. Nine patients (four women) were studied within 1 month of entering a chronic hemodialysis program in the interdialytic period. Plasma malondialdehyde (MDA), red blood cell glutathione (GSH), and catalase (CAT) activity were measured in blood samples obtained before (baseline) and 1, 3, and 24 hours after the administration of Fe (100 mg of Fe saccharate intravenously over 1 hour) or rHuEPO (4,000 U intravenously). One hour before these treatments, patients were administered a single oral dose of MEL (0.3 mg/kg) or placebo. Each patient was studied on four occasions, corresponding to studies performed using either placebo or MEL in association with intravenous Fe and rHuEPO administration. Baseline data showed increased oxidative stress in patients with end-stage renal failure. Increments in oxidative stress induced by Fe were more pronounced at the end of the administration: MDA, baseline, 0.74 +/- 0.09 nmol/mL; 1 hour, 1.50 +/- 0.28 nmol/mL (P: < 0.001); GSH, baseline, 2.51 +/- 0.34 nmol/mg of hemoglobin (Hb); 1 hour, 1.66 +/- 0.01 nmol/mg Hb (P: < 0.001); and CAT activity, baseline, 27.0 +/- 5.7 kappa/mg Hb; 1 hour, 23.3 +/- 4.2 kappa/mg Hb (P: < 0.001). rHuEPO-induced increments in oxidative stress were more pronounced (P: < 0.001) at 3 hours (MDA, 1.24 +/- 0.34 nmol/mL; GSH, 1.52 +/- 0.23 nmol/mg Hb; CAT activity, 18.0 +/- 3.1 kappa/mg Hb). MEL administration prevented the changes induced by Fe and rHuEPO and had no adverse side effects. These studies show that intravenous Fe and rHuEPO in doses commonly used to treat anemia in chronic hemodialysis patients acutely generate significant oxidative stress. Oral MEL prevents such oxidative stress and may be of clinical use

Differential effects of monoterpenes and lovastatin on RAS processing.

Hohl RJ, Lewis K.

J Biol Chem. 1995 Jul 21; 270(29):17508-12.

Limonene and related monoterpenes have been shown to impair the incorporation of mevalonic acid-derived isoprene compounds, that is farnesyl pyrophosphate, into RAS and RAS-related proteins. As farnesylation is critical for RAS's membrane localization and function, the isoprenylation pathways have received attention as potential targets of anti-RAS pharmacologic maneuvers. We have expanded on these prior studies and demonstrate that one of limonene's metabolic derivatives, perillyl alcohol, decreases the levels of antigenic RAS in the human-derived myeloid THP-1 and lymphoid RPMI-8402 cell lines. Both limonene and perillyl alcohol decrease levels of [35S]methionine-labeled RAS proteins in cells that have been pulsed with radiolabeled methionine for 4 h. In contrast, lovastatin, which inhibits hydroxymethylglutaryl coenzyme A reductase and thus depletes cells of farnesyl pyrophosphate, does not diminish levels of total antigenic RAS but rather results in a shift in the RAS protein; levels of farnesylated RAS decrease whereas levels of unmodified/unfarnesylated RAS increase. As limonene and perillyl alcohol do not induce such a shift, we conclude that these monoterpenes decrease farnesylated RAS protein levels by a mechanism that is clearly distinct from that of either depleting cells of farnesyl pyrophosphate or inhibiting the enzyme farnesyl protein transferase that catalyzes the post-translational farnesylation of RAS. Perillyl alcohol decreases antigenic RAS levels but does not decrease levels of another membrane-tethered protein, the alpha subunit of the heterotrimeric G protein. Furthermore, perillyl alcohol decreases the levels of radiolabeled methionine incorporated into immunoprecipitable RAS to a greater extent than it decreases radiolabeled methionine incorporated into total cellular protein. Thus there is some degree of

specificity for the activity of perilyl alcohol to depress RAS levels

Aspirin: the multi-purpose compound not just for headaches anymore.

Knorr J.

Life Extension Magazine 2000 Feb. 2000; *Life Extension Magazine* 2000 Feb 6(2):50.

Advanced prostate cancer activates coagulation: a controlled study of activation markers of coagulation in ambulatory patients with localized and advanced prostate cancer.

Kohli M, Fink LM, Spencer HJ, et al.

Blood Coagul Fibrinolysis. 2002 Jan; 13(1):1-5.

Cancer and increased age are risk factors for coagulation activation. Patients with advanced prostate cancer, which usually presents in the seventh to eighth decade of life, are likely to be at increased risk for thrombosis. We report results of a controlled study of changes in specific and sensitive markers of coagulation activation in patients with prostate cancer. Complete blood count, prothrombin time, partial thromboplastin time, prothrombin fragment 1 + 2 (F1 + 2), thrombin-antithrombin complex (TAT) and quantitative D-dimers (DD) were measured in 30 patients of advanced prostate cancer (androgen ablated), in 30 newly diagnosed localized prostate cancer patients, in 30 healthy age-matched volunteers, and in 20 healthy young volunteers. Plasma F1 + 2 ($P < 0.05$) and DD ($P < 0.05$), but not TAT, were significantly elevated in healthy elderly males (mean age, 77 years) when compared with healthy young volunteers (mean age, 35 years). F1 + 2, TAT and DD were significantly elevated in advanced prostate cancer when compared with healthy age-matched controls ($P < 0.001$). In conclusion, advanced prostate cancer patients have significantly increased levels of sensitive markers of coagulation activation compared with healthy age-matched controls. This data can be used to plan studies to determine the risk of clinically significant coagulopathy and the role of primary prophylaxis in patients with advanced prostate cancer

Subcutaneous heparin treatment increases survival in small cell lung cancer. "Petites Cellules" Group.

Lebeau B, Chastang C, Brechot JM, et al.

Cancer. 1994 Jul 1; 74(1):38-45.

BACKGROUND. A positive influence of anticoagulant treatment in small cell lung cancer (SCLC) has been suggested by experimental and clinical data. **METHODS.** In a multicenter clinical trial, 277 patients with SCLC were randomized either to receive or not to receive subcutaneous heparin injections for 5 weeks at effective doses, which were monitored by blood coagulation tests. All patients received one of the two chemotherapy regimens studied in this trial, for eight courses in the case of patients with complete or partial response, and subsequently were randomized to receive delayed thoracic radiotherapy after these eight courses. **RESULTS.** In comparison to the 139 patients who did not receive heparin, the 138 patients who received anticoagulant treatment obtained better complete response rates (37% vs. 23%, $P = 0.004$), better median survival (317 days vs. 261 days, $P = 0.01$), and better survival rates at 1, 2, and 3 years (40% vs. 30%, 11% vs. 9% and 9% vs. 6%, respectively). At subgroups analysis, the results on survival were obtained for limited forms ($P = 0.03$) but not for extensive diseases ($P = 0.31$). No important bleeding or thrombocytopenia was related to heparin treatment. **CONCLUSIONS.** These results confirm the value of anticoagulant treatment in SCLC, already suspected for warfarin and now proven for heparin, but the modes of administration and the biologic explanations for this activity still warrant further investigation

[An application value of detecting K-ras and p53 gene mutation in the stool and pure pancreatic juice for diagnosis of early pancreatic cancer].

Lu X, Xu T, Qian J.

Zhonghua Yi Xue Za Zhi. 2001 Sep 10; 81(17):1050-3.

OBJECTIVE: To explore new methods for the early diagnosis of pancreatic cancer through detecting of K-ras, p53 mutations in pancreatic juice and stool. **METHODS:** 201 patients in PUMC Hospital from 1994-2000. 5 and 60-control individuals were enrolled. K-ras point mutations were detected by PCR-RFLP, however p53 mutation was detected by PCR-SSCP. **RESULTS:** K-ras mutations in pancreatic juice were found in 87.8% (36/41) of pancreatic cancer, 23.5% (4/17) of benign pancreatic disease. Of 261 stools specimens, amplification was successful in 235 (90.0%). K-ras mutation in stool were found in 88.0% (66/75) of pancreatic cancer 51.1% (24/47) of benign pancreatic disease, 19.6% (9/46) of normal individuals. p53 mutation in pancreatic juice were found in 47.4% (18/38), 12.5% (2/16) of benign pancreatic disease, p53 mutation in stool were found in 37.1%

(23/62), 19.1% (4/12) of chronic pancreatitis. CONCLUSION: K-ras mutation in pancreatic juice has high sensitivity and specificity, so it can be used as an adjunct in the diagnosis of pancreatic cancer. Detection of K-ras mutation combined with p53 mutation in stool can be helpful to screen for pancreatic carcinoma. Combined with serum CA19-9 detection, it might increase the early diagnostic rate of pancreatic carcinoma

Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer.

McGuire WP, Hoskins WJ, Brady MF, et al.

N Engl J Med. 1996 Jan 4; 334(1):1-6.

BACKGROUND. Chemotherapy combinations that include an alkylating agent and a platinum coordination complex have high response rates in women with advanced ovarian cancer. Such combinations provide long-term control of disease in few patients, however. We compared two combinations, cisplatin and cyclophosphamide and cisplatin and paclitaxel, in women with ovarian cancer. **METHODS.** We randomly assigned 410 women with advanced ovarian cancer and residual masses larger than 1 cm after initial surgery to receive cisplatin (75 mg per square meter of body-surface area) with either cyclophosphamide (750 mg per square meter) or paclitaxel (135 mg per square meter over 24 hours). **RESULTS.** Three hundred eighty-six women met all the eligibility criteria. Known prognostic factors were similar in the two treatment groups. Alopecia, neutropenia, fever, and allergic reactions were reported more frequently in the cisplatin-paclitaxel group. Among 216 women with measurable disease, 73 percent in the cisplatin-paclitaxel group responded to therapy, as compared with 60 percent in the cisplatin-cyclophosphamide group ($P = 0.01$). The frequency of surgically verified complete response was similar in the two groups. Progression-free survival was significantly longer ($P < 0.001$) in the cisplatin-paclitaxel group than in the cisplatin-cyclophosphamide group (median, 18 vs. 13 months). Survival was also significantly longer ($P < 0.001$) in the cisplatin-paclitaxel group (median, 38 vs. 24 months). **CONCLUSIONS.** Incorporating paclitaxel into first-line therapy improves the duration of progression-free survival and of overall survival in women with incompletely resected stage III and stage IV ovarian cancer

K-ras mutation: early detection in molecular diagnosis and risk assessment of colorectal, pancreas, and lung cancers--a review.

Minamoto T, Mai M, Ronai Z.

Cancer Detect Prev. 2000; 24(1):1-12.

Multiple genomic alterations are involved in the development of most human cancers. They include alterations in oncogenes, tumor suppressor genes, DNA mismatch repair and excision repair genes. Genetic testing for susceptibility has been a part of the management of patients with well-defined but uncommon hereditary cancers in which certain susceptible gene mutations are determined in the germ line. However, a molecular diagnostic approach to sporadic cancers, which comprise the vast majority of malignant tumors in human beings, is still under development. One of the best characterized tumor-related genes is K-ras, which somatically mutates in several types of sporadic human cancers. Since mutations of this gene occur exclusively in three hot spots (codons 12, 13 and 61), and are frequently detected and well characterized in colorectal, pancreas and lung cancers, molecular diagnosis and susceptibility (risk) assessment targeting K-ras mutations are being developed. For this purpose, sample collection methods that reflect the state of the entire affected organ are important. Clinical samples used for molecular diagnosis and risk assessment include stool and lavage fluid, pancreatic and duodenal juices, and sputum and lavage fluids for colorectal, pancreas and lung cancers, respectively. The reported incidence of K-ras mutations detected in these samples ranges from 7% to 80% for colorectal cancers, 25% to 87% for pancreatic cancers, and 25% to 48% for lung cancers. Incidence of mutations clearly depends on the sensitivity of the method for detecting the mutant K-ras allele, as well as the nature and the quality of the clinical samples. Various methods including plaque hybridization, dot blot hybridization, combined PCR and RFLP or SSCP, and sensitive PCR have been used, and they exhibited high specificity (75 to 100%) in detecting mutations. Molecular analysis is demonstrating promise in assessing susceptibility to, or risk of developing, sporadic cancers

Epidemiological and clinical aspects of nonsteroidal anti-inflammatory drugs and cancer risks.

Moran EM.

J Environ Pathol Toxicol Oncol. 2002; 21(2):193-201.

It is well known that about 70% of cancer cases are due to environmental, dietary, or lifestyle factors. Accordingly, these cases maybe avoided by appropriate modifications. In addition, active chemoprevention has become a major interventional approach following the epidemiological observation of a beneficial effect of nonsteroidal anti-inflammatory drugs (NSAIDs) in colon cancer prevention. This is chiefly due to the inhibition of the cyclooxygenase (COX) enzymes. The COX enzymatic system includes two isoenzymes, COX-1 and COX-2, that convert arachidonic acid to prostaglandins. COX-1 is constitutively expressed and synthesizes cytoprotective prostaglandins in the gastrointestinal tract. COX-2 is inducible by the oncogenes ras and scr and other cytokines; it is overexpressed in human cancer cells in which it stimulates cellular division and angiogenesis and inhibits

apoptosis. NSAIDs restore apoptosis and decrease tumor mitogenesis and angiogenesis. Most cancer cells have been found to exhibit overexpression of COX-2. Epidemiological studies showed a lower risk of developing cancer of the colon, breast, esophagus, and stomach following the ingestion of NSAIDs. The use of NSAIDs in low dose was associated with a statistically significant decrease in the risk of adenomatous polyps and of overt colon cancer. The regressive effects of sulindac on foci of aberrant crypts in the colon (considered to be precursors of adenoma), and on adenocarcinoma of the colon, are of particular interest because this NSAID does not have an inhibitory effect on COX. This may support the view that the antineoplastic effect of NSAIDs may also be due to a mechanism other than COX-2 inhibition. In breast cancer, large cohort studies reported a 40 to 50% reduced risk of developing cancer, a smaller size of the primary tumor, and a reduction in the number of involved axillary lymph nodes. Similar findings have been reported in the esophagus and stomach, but not in gastric cardia adenocarcinoma. The recent development of selective COX-2 inhibitors resulted in better clinical tolerance than that associated with NSAIDs in general, with the absence of gastrointestinal side effects known to occur after the inhibition of COX-1. Encouraging results have been obtained with these new agents in familial adenomatous polyposis, colon, breast, and prostate cancer

Anticoagulants in thrombosis and cancer: the missing link.

Mousa SA.

Expert Rev Anticancer Ther. 2002 Apr; 2(2):227-33.

Many cancer patients reportedly have hypercoaguable state, with recurrent thrombosis due to the impact of cancer cells and chemotherapy on the coagulation cascade. A number of retrospective studies showed that cancer patients are at higher risk of developing venous thromboembolism. In addition to the pathological mechanisms associated with tumor-mediated increase in thrombotic events, cancer therapies including chemotherapy, immobilization, cancer surgery and the use of central venous catheters contribute toward a hypercoaguable state and are therefore independent risk factors of venous thromboembolism in cancer patients. Studies have demonstrated that unfractionated heparin or low molecular weight heparin (LMWH) interferes with various processes involved in tumor growth and metastasis. These processes might include fibrin formation, binding of heparin to angiogenic growth factors--such as basic fibroblast growth factor and VEGF--modulation of tissue factor, release of tissue factor pathway inhibitor and other mechanisms. Clinical trials have suggested an improved efficacy of LMWH, as compared with UFH on the survival of cancer patients with deep vein thrombosis. Similarly, the impact of warfarin on the survival of cancer patients with thromboembolic disorders was demonstrated. Recent studies from our laboratory defined the role of the LMWH (tinzaparin), warfarin, antifactor VIIa and recombinant tissue factor pathway inhibitor in the modulation of angiogenesis, tumor growth and tumor metastasis

Risk of cardiovascular events associated with selective COX-2 inhibitors.

Mukherjee D, Nissen SE, Topol EJ.

JAMA. 2001 Aug 22; 286(8):954-9.

Atherosclerosis is a process with inflammatory features and selective cyclooxygenase 2 (COX-2) inhibitors may potentially have antiatherogenic effects by virtue of inhibiting inflammation. However, by decreasing vasodilatory and antiaggregatory prostacyclin production, COX-2 antagonists may lead to increased prothrombotic activity. To define the cardiovascular effects of COX-2 inhibitors when used for arthritis and musculoskeletal pain in patients without coronary artery disease, we performed a MEDLINE search to identify all English-language articles on use of COX-2 inhibitors published between 1998 and February 2001. We also reviewed relevant submissions to the US Food and Drug Administration by pharmaceutical companies. Our search yielded 2 major randomized trials, the Vioxx Gastrointestinal Outcomes Research Study (VIGOR; 8076 patients) and the Celecoxib Long-term Arthritis Safety Study (CLASS; 8059 patients), as well as 2 smaller trials with approximately 1000 patients each. The results from VIGOR showed that the relative risk of developing a confirmed adjudicated thrombotic cardiovascular event (myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, and transient ischemic attacks) with rofecoxib treatment compared with naproxen was 2.38 (95% confidence interval, 1.39-4.00; $P = .002$). There was no significant difference in cardiovascular event (myocardial infarction, stroke, and death) rates between celecoxib and nonsteroidal anti-inflammatory agents in CLASS. The annualized myocardial infarction rates for COX-2 inhibitors in both VIGOR and CLASS were significantly higher than that in the placebo group of a recent meta-analysis of 23 407 patients in primary prevention trials (0.52%): 0.74% with rofecoxib ($P = .04$ compared with the placebo group of the meta-analysis) and 0.80% with celecoxib ($P = .02$ compared with the placebo group of the meta-analysis). The available data raise a cautionary flag about the risk of cardiovascular events with COX-2 inhibitors. Further prospective trial evaluation may characterize and determine the magnitude of the risk

Proceedings of the American Society of Clinical Oncology.

Nagourney RA.

1995;

Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients.

Nagourney RA, Link JS, Blitzer JB, et al.

J Clin Oncol. 2000 Jun; 18(11):2245-9.

PURPOSE: To determine the safety and efficacy of gemcitabine plus cisplatin for patients with relapsed adenocarcinoma of the breast. **PATIENTS AND METHODS:** Previously treated patients with adenocarcinoma of the breast received cisplatin (30 mg/m²) plus gemcitabine (1,000 mg/m²) on days 1, 8, and 15 of each 28-day cycle, which was changed after patient no. 12 to cisplatin (30 mg/m²) plus gemcitabine (750 mg/m²) days 1 and 8 of each 21-day cycle. **RESULTS:** Of 30 patients, three (10%) had complete and 12 (40%) had partial responses, for an overall response rate of 50%. Two objective responses were observed among the four patients accrued after relapse that followed high-dose/stem-cell therapies. The median time to progression was 14 weeks. The median time to progression for objective responders was 23.5 weeks, with a range of 8 to 68 weeks. Toxicities included grades III and IV neutropenia in 13%, anemia in 6%, thrombocytopenia in 31%, grade III nausea in 4%, and grade II peripheral neuropathy in 2% of 151 treatment cycles. Moderate alopecia occurred in four patients. There were no treatment-related deaths. **CONCLUSION:** Cisplatin plus gemcitabine is active and tolerable for patients with relapsed breast cancer. Responses observed in previously treated patients, including high-dose/stem-cell failures, indicate activity in otherwise drug-refractory patients

Suppression of intestinal polyp development by nimesulide, a selective cyclooxygenase-2 inhibitor, in Min mice.

Nakatsugi S, Fukutake M, Takahashi M, et al.

Jpn J Cancer Res. 1997 Dec; 88(12):1117-20.

Nonsteroidal anti-inflammatory drugs (NSAIDs) suppress colon carcinogenesis in man and experimental animals. However, conventional NSAIDs inhibit both cyclooxygenase (COX) isoforms, COX-1 and COX-2, and cause gastrointestinal side-effects. Nimesulide, a selective inhibitor of COX-2, is much less ulcerogenic. We, therefore, examined its influence on the development of intestinal polyps in Min mice. Female Min mice at 4 weeks old were given 400 ppm nimesulide in their diet for 11 weeks. This treatment resulted in a significant reduction of the numbers of both small and large intestinal polyps, the total being 52% of that in untreated control Min mice. The size of the polyps in the nimesulide-treated group was also significantly decreased. The results suggest that nimesulide is a good candidate as a chemopreventive agent for human colon cancer with low toxicity

Beyond Aspirin.

Newmark T.

2000;

Angiogenesis Inhibitors in Cancer Research.

NIH/NCI.

NIH/NCI Angiogenesis Inhibitors in Cancer Research 1998 Jul 7 Bethesda, MD: National Cancer Institute ([Http://Www Slip Net/~Mcdavis/Database/Angio163 Htm](http://www.SlipNet/~Mcdavis/Database/Angio163 Htm)). 1998;Jul 7

Therapies of the Future: New Molecular Targets for Cancer Therapy.

Oliff A.

1996

Docetaxel (Taxotere) in hormone-refractory prostate cancer.

Petrylak DP.

Semin Oncol. 2000 Apr; 27(2 Suppl 3):24-9.

Considerations of both molecular biology and data from in vitro studies suggest a potential for the combination of docetaxel (Taxotere; Rhone-Poulenc Rorer, Antony, France) with estramustine in the treatment of patients with hormone-refractory prostate cancer. Based on data from two phase I studies, the docetaxel dose recommended for phase II study in combination with estramustine in minimally and extensively pretreated patients is 70 mg/m² and 60 mg/m², respectively. The dose-limiting toxicity was neutropenia. In one phase I study, 63% of the 34 patients treated showed at least a 50% decline in prostate-specific antigen. An objective response was seen in 28% of patients with measurable disease, and overall median survival (22.8 months) is highly encouraging. In the second study, 82% of 17 patients showed a greater than 50% decline in prostate-specific antigen and, at the 70 mg/m² dose level, two of six patients showed prostate-specific antigen normalization. Phase II studies have demonstrated more than 50% declines in 59% to 88% of patients treated at 70 mg/m². Although reduction of the dose of estramustine appears to result in a somewhat lower response rate, the contribution made by estramustine to the efficacy of the estramustine/docetaxel combination must be established by randomized trials. Dexamethasone, however, does not appear to significantly contribute to the response rate of estramustine and docetaxel. Phase III studies comparing docetaxel plus estramustine with mitoxantrone plus corticosteroids are currently being planned. If the promise of docetaxel hormone-refractory prostate cancer is realized, it may be appropriate to design clinical trials that evaluate docetaxel-based regimens as adjuvant therapy in patients who are at a high risk for relapse after definitive local therapy

Chemotherapy for androgen-independent prostate cancer.

Petrylak DP.

Semin Urol Oncol. 2002 Aug; 20(3 Suppl 1):31-5.

While men with metastatic prostate cancer frequently show a good initial response to androgen ablation, few options have been available for progressive hormone-refractory prostate cancer, and survival following chemotherapy has not exceeded 9 to 12 months. The combination of prednisone and mitoxantrone has significant palliative effects on bone pain but does not extend survival. The combination of estramustine phosphate (EMP) with the taxanes paclitaxel or docetaxel produces greater than additive cytotoxicity in vivo, and phase I and II studies of taxane-based therapy demonstrate improved survival in hormone-refractory prostate cancer compared to historical controls. Docetaxel appears to have relatively high activity as a single agent and in combination with EMP. Further studies are needed to clarify the optimum dose of EMP, taking into account potential cardiovascular toxicity. Phase III studies of its combination with docetaxel are in progress

Colon cancer: a role for cyclo-oxygenase-2-specific nonsteroidal anti-inflammatory drugs.

Reddy BS, Rao CV.

Drugs Aging. 2000 May; 16(5):329-34.

Large bowel cancer is not only the third most frequent cancer in the world but is one of the most common human malignancies in Western countries, including North America. In recent years, multidisciplinary research in epidemiology, molecular biology, and laboratory animal model studies have contributed much to our understanding of the aetiology of this cancer; more importantly, it has enabled us to devise preventive strategies. Several epidemiological studies have detected a 40 to 50% decrease in risk of colorectal cancer in individuals who regularly use aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical trials with NSAIDs in patients with familial adenomatous polyposis have demonstrated that treatment with NSAIDs caused regression of pre-existing adenomas. Preclinical efficacy studies have provided scientifically sound evidence as to how NSAIDs act to retard, block, or reverse colonic carcinogenesis. Equally exciting are opportunities for effective chemoprevention with selective cyclo-oxygenase-2 inhibitors in a variety of animal models of colon cancer. Selective cyclo-oxygenase-2 inhibitors such as celecoxib have been proven to be effective chemopreventive agents against colonic carcinogenesis with minimal gastrointestinal toxicity. Our exploration of the multistep process of carcinogenesis has provided substantial insights into the mechanisms by which anti-inflammatory agents modulate these events. There is growing optimism for the view that realisation of preventive concepts in large bowel cancer will also serve as a model for preventing malignancies of the prostate and breast

Increased alpha 1 antitrypsin, decreased systemic fibrinolysis, hypercoagulable state and increased fibrin split products in patients with lung cancer.

Samuels AJBHRSSB.

Proc Am Soc Clin Oncol. 1975;(16):238.

A Dietary Road Map.

Sears B.

1995;

Acquired coronary angiogenesis after myocardial infarction.

Shammas NW, Moss AJ, Sullebarger JT, et al.

Cardiology. 1993; 83(3):212-6.

Acquired coronary artery microvascular fistulas have been reported in only a few patients after myocardial infarction. We describe 1 patient in whom serial coronary angiography demonstrated the development of coronary angiogenesis at the site of an old myocardial infarction. The area of neovascularity was associated with a large apical left ventricular thrombus. This finding suggests that growth-promoting mitogens are present in myocardium and thrombus and that angiogenesis occurs in some patients following myocardial infarction

The relationship between cyclooxygenase-2 expression and colorectal cancer.

Sheehan KM, Sheahan K, O'Donoghue DP, et al.

JAMA. 1999 Oct 6; 282(13):1254-7.

CONTEXT: Epidemiological studies have implicated the inducible form of cyclooxygenase (COX-2) in the pathogenesis of colorectal cancer; however, its role is not fully understood. OBJECTIVE: To examine the relationship between the expression of COX-2 in human colorectal cancer and patient survival. DESIGN: Patients diagnosed as having colorectal cancer were evaluated and followed up for up to 9.4 years (median follow-up, 2.7 years). Tumor sections were stained for COX-2 using a rabbit polyclonal antibody raised against human COX-2. The extent of COX-2 staining was graded by 2 observers blinded to outcome. Preabsorption of the anti-COX-2 antibody with a COX-2 peptide abolished the staining, demonstrating the specificity of the assay. SETTING: Gastrointestinal unit of a large general teaching hospital in Dublin, Ireland. PARTICIPANTS: Seventy-six patients (median age, 66.5 years) with colorectal cancer (Dukes tumor stage A, n = 9; Dukes B, n = 30; Dukes C, n = 25; Dukes D, n = 12) whose diagnosis was made between 1988 and 1991. Fourteen normal colon biopsies were stained for COX-2 as controls. MAIN OUTCOME MEASURES: Survival in years following diagnosis compared by extent of COX-2 epithelial staining (grade 1, <1%; grade 2, 1%-19%; grade 3, 20%-49%; grade 4, > or = 50%), Dukes stage, tumor size, and lymph node metastasis. RESULTS: COX-2 was found in tumor epithelial cells, inflammatory cells, vascular endothelium, and/or fibroblasts. The extent of epithelial staining was heterogeneous, varying markedly among different tumors. Normal tissue adjacent to the tumors also stained weakly for COX-2. No COX-2 was detected in control tissue samples. The Kaplan-Meier survival estimate was 68% in patients who had grade 1 tumor epithelial staining compared with 35% in those with higher grades combined (log-rank $\chi^2 = 5.7$; $P = .02$). Greater expression of COX-2 correlated with more advanced Dukes stage (Kendall tau-b, 0.22; $P = .03$) and larger tumor size (Kendall tau-b, 0.21; $P = .02$) and was particularly evident in tumors with lymph node involvement (Kendall tau-b, 0.26; $P = .02$). CONCLUSIONS: Our data indicate that COX-2 expression in colorectal cancer may be related to survival. These data add to the growing epidemiological and experimental evidence that COX-2 may play a role in colorectal tumorigenesis

Inhibition of deoxyglucose uptake in MCF-7 breast cancer cells by 2-methoxyestrone and 2-methoxyestrone-3-O-sulfamate.

Singh A, Purohit A, Hejaz HA, et al.

Mol Cell Endocrinol. 2000 Feb 25; 160(1-2):61-6.

Most cancer cells are dependent on glucose uptake to fulfil their energy requirements. In the present investigation we have examined the ability of 2-methoxyestrone (2-MeOE1), 2-methoxyestradiol (2-MeOE2), 2-methoxyestrone-3-O-sulfamate (2-MeOEMATE), and a number of related compounds, to inhibit 2-deoxy-D-[1-(3)H]-glucose uptake in MCF-7 breast cancer cells. Glucose uptake was shown to be linear with respect to cell number and time over a 5-35min period. 2-MeOE2, 2-MeOE1 and 2-MeOEMATE inhibited glucose uptake by 25-49% at 10 microM. 2-Hydroxyestradiol and estrone sulfate had little effect on glucose uptake, whereas estrone glucuronide inhibited uptake by 29%. There is evidence that 2-methoxyestrogens may exert an anti-mitotic effect on cells by stabilizing microtubules in a similar manner to that of paclitaxel. We therefore examined the effect of exposing cells to 2-MeOEMATE or paclitaxel for 24 h on basal or insulin stimulated glucose uptake. Using these conditions, 2-MeOEMATE and paclitaxel inhibited basal glucose uptake by 50 and 22%, respectively, and insulin stimulated uptake by 36 and 51%, respectively. The development of drugs that can inhibit glucose uptake could have therapeutic potential for the treatment of breast cancer

Cancer-related anemia: its causes and characteristics.

Spivak JL.

Semin Oncol. 1994 Apr; 21(2 Suppl 3):3-8.

Under normal circumstances, the circulating red blood cell mass is maintained at a level that is constant in each individual, although that level may vary by more than 10% among individuals of the same age and gender. At normal ambient oxygen tension, two factors determine the circulating red blood cell mass: red blood cell life span, which is finite and in humans approximates 120 days; and the rate of effective red blood cell production. To maintain a constant red blood cell mass, therefore, approximately 20 mL of red blood cells must be produced each day to replace those red blood cells lost from the circulation through senescence. Anemia, which may be defined functionally as lack of sufficient red blood cells to maintain adequate tissue oxygenation, develops when the demand for new red blood cells exceeds the capacity of the bone marrow to produce them. This may be due to excessive red blood cell destruction, impaired red blood cell production, bleeding, or any combination of these. Acquired anemia is always a consequence of another disorder, which must be identified to ensure that the corrective therapy is appropriate. In patients with solid tumors, multiple mechanisms for causing anemia have been identified: blood loss that is either intrinsic or iatrogenic; nutritional deficiencies involving primarily iron or folic acid; hemolysis (autoimmune, traumatic, or drug-induced); bone marrow failure due to tumor encroachment, myelofibrosis, or marrow necrosis; infection; inflammation; or simply the presence of a cancer elsewhere in the body. The three noted causes of marrow failure share a common denominator: impaired production of erythropoietin. For any degree of anemia, a patient with cancer produces much less erythropoietin than expected and, therefore, cannot compensate for impaired red blood cell production. Inflammation or infection can exacerbate this situation. Indeed, anemia in patients with cancer appears to behave much like that in patients with chronic renal failure who become anemic because of the inability of the kidneys to produce erythropoietin adequately. The cause of impaired erythropoietin production in patients with cancer who have anemia is not entirely understood, but may be due in part to the production of inflammatory cytokines in response to the tumor. Such cytokines also would be expected to blunt the ability of the bone marrow to respond to the available circulating erythropoietin. (ABSTRACT TRUNCATED AT 400 WORDS)

Understanding angiogenesis and its clinical applications.

Suh DY.

Ann Clin Lab Sci. 2000 Jul; 30(3):227-38.

Angiogenesis is the growth of new vessels from pre-existing blood vessels. Angiogenesis is critical during embryogenesis but occurs minimally in healthy adults, except in wound repair, inflammation, female reproductive organs, and pathologic conditions. Various growth factors and proteins, elements of the extracellular matrix, components of the coagulation/fibrinolytic system, and platelets interact with the endothelial cells and pericytes of blood vessels to regulate angiogenesis. Characterization of angiogenic factors has revealed that remodeling of the extracellular matrix occurs during angiogenesis, mediated by integrins that are found on the endothelial cell surface membrane. Counter-regulatory antiangiogenic proteins and molecules that show an intricate balance in the regulation of angiogenesis have also been characterized. Components of the coagulation/fibrinolysis cascade also play a critical role in angiogenesis. Elucidation of the mechanisms of angiogenesis has led to better understanding of certain disease states. Ongoing studies are evaluating the stimulation of angiogenesis to treat ischemic disorders, and the inhibition of angiogenesis to prevent abnormal proliferation in malignant and non-malignant disorders

Relationship of glutathione depletion and inhibition of glutathione-S-transferase activity to the antimetabolic properties of estramustine.

Tew KD, Woodworth A, Stearns ME.

Cancer Treat Rep. 1986 Jun; 70(6):715-20.

A depletion of intracellular glutathione (GSH) is accompanied by a subsequent inhibition of GSH-S-transferase activity in a DU145 human prostatic carcinoma cell line treated with cytotoxic concentrations of estramustine. When GSH depletion reached approximately 50% of normal (approximately 2 hours after 10 microM estramustine), the mitotic index of logarithmically dividing cultures began to increase. A linear increase from 3.14% to 22.5% occurred during the period of 2-24 hours following 10 microM estramustine. Morphological studies showed that mitotic figures accumulated in metaphase and had abnormalities consistent with spindle malformation. Nocodazole and cytochalasin B also possess anticytoskeletal properties, but had little effect upon the intracellular levels of GSH or its associated transferase enzymes. The constituent moieties of estramustine, estradiol, and nor-mechlorethamine had effects on thiol metabolism which were dissimilar from estramustine, confirming previous findings that the unmetabolized parent drug is responsible for pharmacological activity. Estramustine had no effect upon GSH reductase activity, suggesting that drug toxicity was not a general thiol phenomenon. Buthionine sulfoximine decreased intracellular GSH in DU145 cells and enhanced the cytotoxic potential of estramustine in this cell line. The anticytoskeletal and antimetabolic

properties of estramustine may be enhanced by the drug-induced GSH imbalance and subsequent effects on GSH-S-transferase enzymes

Hormone-independent, non-alkylating mechanism of cytotoxicity for estramustine.

Tew KD, Stearns ME.

Urol Res. 1987; 15(3):155-60.

Over two decades, experience with estramustine has provided limited data which support an estrogenic mechanism of action and no data which indicate the nitrogen mustard involvement in the cytotoxic properties of the drug. Consideration of the carbamate-ester portion of estramustine supports the pharmacokinetic evidence that estramustine has a long half life since enzymatic hydrolysis of the carbamate is an uncommon event. Using a variety of immunocytochemical and cellular morphology procedures, estramustine per se has been found to express anti-cytoskeletal properties through non-covalent binding to microtubule associated proteins (MAP's). In both fish erythrocytes and in dividing human prostatic carcinoma cells, estramustine exerts an antimicrotubule effect at micromolar concentrations. Thus, estramustine possesses unique pharmacology and protein binding specificity. As such, it should not be classified as an alkylating agent. The estrogenic effects, while possibly of relevance to clinical administration, are not the primary mechanism by which the drug exerts cytotoxicity

Preclinical and clinical perspectives on the use of estramustine as an antimitotic drug.

Tew KD, Glusker JP, Hartley-Asp B, et al.

Pharmacol Ther. 1992 Dec; 56(3):323-39.

A variety of cell biological, pharmacological, crystallographic and clinical approaches have indicated that the antimitotic drug estramustine has interesting and unusual properties. Although designed as an alkylating agent, the marked stability of the carbamate linkage to the steroid carrier molecule prevents the formation of alkylating intermediates. The affinity of the parent molecule for microtubule associated proteins and the concomitant antimicrotubule activity have cytotoxic consequences in tumor cells. Both preclinical and clinical studies of estramustine in combination with other antimicrotubule agents have shown that this approach has great potential to achieve therapeutic advantage, especially in disease states such as hormone refractory prostate cancer

Cyclooxygenase regulates angiogenesis induced by colon cancer cells.

Tsuji M, Kawano S, Tsuji S, et al.

Cell. 1998 May 29; 93(5):705-16.

To explore the role of cyclooxygenase (COX) in endothelial cell migration and angiogenesis, we have used two in vitro model systems involving coculture of endothelial cells with colon carcinoma cells. COX-2-overexpressing cells produce prostaglandins, proangiogenic factors, and stimulate both endothelial migration and tube formation, while control cells have little activity. The effect is inhibited by antibodies to combinations of angiogenic factors, by NS-398 (a selective COX-2 inhibitor), and by aspirin. NS-398 does not inhibit production of angiogenic factors or angiogenesis induced by COX-2-negative cells. Treatment of endothelial cells with aspirin or a COX-1 antisense oligonucleotide inhibits COX-1 activity/expression and suppresses tube formation. Cyclooxygenase regulates colon carcinoma-induced angiogenesis by two mechanisms: COX-2 can modulate production of angiogenic factors by colon cancer cells, while COX-1 regulates angiogenesis in endothelial cells

Cyclooxygenase-2 expression is up-regulated in human pancreatic cancer.

Tucker ON, Dannenberg AJ, Yang EK, et al.

Cancer Res. 1999 Mar 1; 59(5):987-90.

A large body of evidence suggests that cyclooxygenase-2 (COX-2) is important in gastrointestinal cancer. The purpose of this study was to determine whether COX-2 was expressed in adenocarcinoma of the human pancreas. Quantitative reverse transcription-PCR, immunoblotting, and immunohistochemistry were used to assess the expression of COX-2 in pancreatic tissue. Levels of COX-2 mRNA were increased by >60-fold in pancreatic cancer compared to adjacent nontumorous tissue. COX-2 protein was present in 9 of 10 cases of adenocarcinoma of the pancreas but was undetectable in nontumorous pancreatic tissue. Immunohistochemical analysis showed that COX-2 was expressed in malignant epithelial cells. In cultured human pancreatic cancer cells, levels of COX-2 mRNA and protein were induced by treatment with tumor-promoting phorbol esters.

Taken together, these results suggest that COX-2 may be a target for the prevention or treatment of pancreatic cancer

Cyclooxygenase-2 expression is related to prostaglandin biosynthesis and angiogenesis in human gastric cancer.

Uefuji K, Ichikura T, Mochizuki H.

Clin Cancer Res. 2000 Jan; 6(1):135-8.

Although recent studies have demonstrated that cyclooxygenase (COX)-2 is overexpressed in various cancers including gastric cancer, the mechanisms underlying the contribution of COX-2 to tumorigenesis and tumor promotion still remain unclear. To determine the role of COX-2, we investigated the COX-2 expression, the prostaglandin (PG) levels, and the microvessel density in 42 patients with primary gastric adenocarcinoma. COX-2 protein was over-expressed in 31 (74%) of 42 gastric cancers based on an immunoblot analysis. The intensity of COX-2 expression was found to significantly correlate with lymph node involvement. The COX-2 overexpressed cases showed significantly elevated levels of prostaglandin E2 (PGE2) in cancer tissues in comparison with the normal gastric mucosa by an immunoassay (201 +/- 90 versus 161 +/- 57 ng/mg protein; P < 0.05). However, the COX-2 overexpression was not related to the levels of thromboxane B2 and 6-keto-prostaglandin F1alpha. The density of microvessel immunostained with CD34 was significantly higher in patients demonstrating COX-2 overexpression than in those without such expression (63 +/-21 versus 45 +/- 17/200 x; P < 0.01). Our data thus suggested COX-2 overexpression to be associated with increased PGE2 biosynthesis and angiogenesis in gastric cancer, which indicates that COX-2 may play a role in the development of gastric cancer

Occurrence of ras mutations in human lung cancer. Minireview.

Vachtenheim J.

Neoplasma. 1997; 44(3):145-9.

Members of ras family of oncogenes, when activated by a point mutation, have been implicated in many types of human cancers. In several types of human solid tumors, point mutations of the K-ras gene are relatively frequent. Among lung cancers, a subset of non-small cell lung carcinomas, mostly adenocarcinomas, contains activated K-ras. The examination of K-ras mutations in samples obtained for diagnostic reasons, such as bronchial biopsies or bronchoalveolar lavage fluid, may be used as a supplement in the early diagnosis of lung adenocarcinoma

Dysregulation of melatonin metabolism in chronic renal insufficiency: role of erythropoietin-deficiency anemia.

Vaziri ND, Oveisi F, Reyes GA, et al.

Kidney Int. 1996 Aug; 50(2):653-6.

Chronic renal failure (CRF) is associated with a variety of neurological and endocrine disorders. In this study, we examined the effect of CRF and the associated anemia on circadian variation of pineal hormone, melatonin. Animals were studied six weeks after 5/6 nephrectomy (CRF group, N = 26) or sham operation (control group, N = 28). A group of erythropoietin-treated CRF animals (CRF/EPO, N = 6) was included to discern the possible role of EPO-deficiency anemia. Compared with the normal control group, the CRF group showed a marked attenuation of the nocturnal surge in serum melatonin concentration. In addition, pineal gland melatonin content measured after a 12-hour dark cycle (< or = 2 lux) was significantly depressed in the CRF group when compared to that obtained in the control group. However, the CRF animals exhibited appropriate suppression of serum concentration and pineal tissue melatonin content in response to bright light (> or = 2500 lux). Administration of EPO led to correction of the CRF anemia and a marked improvement of the defective nocturnal rhythm of serum melatonin. Based on our results, experimental CRF is associated with a marked attenuation of the normal nocturnal surge of serum melatonin concentration. Regular EPO administration results in the correction of anemia and substantial reversal of this abnormality suggesting the partial role of EPO deficiency. The possible role of melatonin dysregulation in the pathophysiology of CRF and the potential value of melatonin supplementation in this condition is uncertain and awaits future investigations

Effect of low molecular weight heparin (Certoparin) versus unfractionated heparin on cancer survival following breast and pelvic cancer surgery: A prospective randomized double-blind trial.

von Tempelhoff GF, Harenberg J, Niemann F, et al.

Int J Oncol. 2000 Apr; 16(4):815-24.

Recent studies suggest that low molecular weight heparin (LMW heparin) therapy in malignancy may improve cancer survival

following surgical resection. We studied prospectively whether cancer mortality during follow-up in women with previously untreated breast, and pelvic cancer is reduced in those who randomly received LMW heparin (Certoparin) compared to patients given unfractionated heparin (UF heparin) for thrombosis prophylaxis during primary surgery. In a prospective, randomized, double-blind clinical trial, 160 patients received Certoparin and 164 UF heparin until post-operatively day 7. Survival estimations are based on the outcome data from a subset of 140 LMW heparin - and 147 UF heparin recipients. Long-term survival in the Certoparin group compared to the UF heparin group was significantly improved after 650 days ($P=0.0066$) but not thereafter when analysis was performed on all cancer cell types combined. In the probability estimates survival benefit within this time was restricted to patients with pelvic cancer but was not observed in breast cancer. However, in breast cancer patients who received LMW heparin the impact of classical tumor prognostic markers was statistically significant after 1,050 days but not after 650 days. Thus, breast cancer patients with unfavorable prognosis seem to benefit in terms of survival advantage from LMW heparin within the 650 days after surgery. These results suggest that improvement in cancer survival can be achieved after even a short course of treatment with LMWH (compared to UFH) given for DVT prophylaxis in the post-operative period. An effect of UFH on disease outcome is not excluded. Further definitive trials of LMWH vs. placebo for cancer outcome (rather than DVT) using doses and schedules that may be more optimal are indicated

Suppression of invasion and MMP-9 expression in NIH 3T3 and v-H-Ras 3T3 fibroblasts by lovastatin through inhibition of ras isoprenylation.

Wang IK, Lin-Shiau SY, Lin JK.

Oncology. 2000 Sep; 59(3):245-54.

Lovastatin, a hydroxymethylglutaryl coenzyme A reductase inhibitor, was found to block the synthesis of cholesterol and to affect posttranslational modification or isoprenylation, which is essential for membrane localization and biological activity of several proteins including Ras in the signal transduction pathway. Ras activates a multitude of downstream activities with roles in cellular processing, including invasion and metastasis. We investigated the anti-invasive activity of lovastatin in NIH 3T3 and v-H-Ras-transformed NIH 3T3 (v-H-Ras 3T3) cells. Lovastatin suppressed cell invasion in vitro in a dose-dependent manner. By zymographic assay, a decrease in matrix metalloproteinase-9 (MMP-9) activity but not matrix metalloproteinase-2 (MMP-2) activity by lovastatin was detected. RT-PCR demonstrated a reduction in gene expression of MMP-9 after treatment with lovastatin. To confirm the lovastatin-induced down-regulation of MMP-9 expression, we transfected an MMP-9/luciferase reporter vector, under MMP-9 promoter control, into both NIH 3T3 and v-H-Ras 3T3. A reduction in luciferase activity was observed with lovastatin treatment. In addition, lovastatin also reduced AP-1 and NFkappaB binding activities. These anti-invasive features were attenuated by the presence of mevalonate. These results suggest that down-regulation of MMP-9 contributes to the anti-invasive activity of lovastatin. Furthermore, we added exogenous mevalonate, which enhances the potency of cell invasion, and Ras farnesyltransferase inhibitor (manumycin A), which inhibits the potency of cell invasion. In accordance, Western blot analysis showed that lovastatin decreased membrane localization of Ras proteins. These data indicate that the anti-invasion activity of lovastatin happens through a decrease in Ras isoprenylation and functions

Prediction of drug resistance in cancer chemotherapy: the Kern and DiSC assays.

Weisenthal LM, Kern DH.

Oncology (Huntingt). 1991 Sep; 5(9):93-103.

In the opinion of the authors, good medical practice demands the avoidance of ineffective therapies and good cancer chemotherapy generally demands the avoidance of inactive drugs. The authors present their viewpoint that randomized trials are not required to prove that physicians should not administer inactive drugs and that existing cell culture assays are acceptably accurate in identifying inactive drugs. They describe and advocate the use of two such tests to aid in choosing between different forms of therapy that would otherwise be equally acceptable in the absence of test information. Strengths, weaknesses, and applications of the assays are discussed

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Effect of warfarin anticoagulation on survival in carcinoma of the lung, colon, head and neck, and prostate. Final report of VA Cooperative Study #75.

Zacharski LR, Henderson WG, Rickles FR, et al.

Cancer. 1984 May 15; 53(10):2046-52.

VA Cooperative Study #75 was established to test in a controlled, randomized trial the hypothesis that warfarin anticoagulation would favorably affect the course of certain types of malignancy. No differences in survival were observed between warfarin-treated and control groups for advanced non-small cell lung, colorectal, head and neck and prostate cancers. However, warfarin therapy was associated with a significant prolongation in the time to first evidence of disease progression ($P = 0.016$) and a significant improvement in survival ($P = 0.018$) for patients with small cell carcinoma of the lung, including the subgroup of patients with disseminated disease at the time of randomization ($P = 0.013$). A trend toward improved survival with warfarin treatment was observed for the few patients admitted to this study with non-small cell lung cancer who had minimal disease at randomization. These results suggest that warfarin, as a single anticoagulant agent, may favorably modify the course of some, but not all, types of human malignancy, among which is small cell carcinoma of the lung. Further trials of warfarin may be indicated in patients with limited disease who have cell types that failed to respond when advanced disease was present

Small cell carcinoma of the lung: interaction with the blood coagulation mechanism and treatment with anticoagulants.

Zacharski LR.

Onkologie. 1987 Aug; 10(4):264-70.

Studies of malignancy in experimental animal models have indicated that cause-effect relationships exist between coagulation activation and cancer progression. Evidence for coagulation activation in human malignancy together with favorable results from pilot clinical trials led to the establishment of a prospective, randomized therapeutic trial of warfarin in cancer. A statistically significant prolongation of survival was observed in patients with small cell carcinoma of the lung entered into this study. Demonstration of an initiator of coagulation activation together with coagulation factor intermediates and fibrin in situ associated with viable tumor cells in small cell carcinoma of the lung is consistent with the hypothesis that tumor-initiated thrombin formation might contribute to progression of this tumor type. These observations suggest novel experimental treatment strategies for small cell carcinoma of the lung. Warfarin anticoagulation may be of value in the treatment of certain other types of malignancy

Occurrence of blood coagulation factors in situ in small cell carcinoma of the lung.

Zacharski LR, Memoli VA, Rousseau SM, et al.

Cancer. 1987 Dec 1; 60(11):2675-81.

Through immunohistochemical techniques, blood coagulation factors were identified in situ in fresh frozen sections of small cell carcinoma of the lung. Prothrombin/thrombin, factor VII, factor X, and antithrombin III were present in intercellular spaces and associated with tumor cells. Factor IX, factor XI, prekallikrein, and high molecular weight kininogen were identified as being associated with tumor cells but did not exist in intercellular spaces. Variable connective tissue staining but no tumor-related staining was observed for factor V, factor VIII-related antigen, factor XII, the B subunit of factor XIII, alpha 1-antitrypsin, alpha 2-macroglobulin, or alpha 2-antiplasmin. Neither consecutive tissue nor the tumor manifested platelet Ib and IIbIIIa surface glycoproteins. These divergent staining patterns suggested that the detected clotting factors had not merely diffused from permeabilized blood vessels, but were selectively localized in situ. While conditions may exist within tumor tissue that both retard and promote thrombin generation, we propose that interactions between the observed coagulation factors ultimately lead to local thrombin formation, which is responsible for the conspicuous fibrin deposits already described in small cell carcinoma of the lung. Thrombin formed locally might contribute to progression of this tumor. Inhibition of local thrombin formation by warfarin therapy could explain the beneficial effects of warfarin therapy in treating small cell carcinoma of the lung

[Coagulation disorders in tumors and hemoblastoses].

Zurborn KH, Bernsmeier R, Schamerowski F, et al.

Onkologie. 1982 Aug; 5(4):186-90.

Thromboembolic and haemorrhagic complications are not rarely seen in the course of malignant diseases. The underlying coagulation disorders were investigated by means of coagulation analysis in 61 patients with solid tumors and 60 control persons as well as 51 patients with leukemia and 50 control persons. As a cause for the thrombotic diathesis in patients with solid tumors and leukemias can be demonstrated a hypercoagulability (shortened PTT and raised factor VIII activity). In addition we found a raised level of fibrinogen, a hypofibrinolysis (prolonged euglobulin lysis time) and in increased platelet aggregation in patients with solid tumors. Predominantly bleeding complications in leukemias are caused by thrombopenia. Another reason, however, may be an activated fibrinolysis or a clot instability because of the reduction of factor XIII. Pathogenetic mechanisms, underlying the tumor induced coagulation disorders, as for example the release of tumor cell thromboplastins from malignant cells are discussed

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