RETINOIDI

IN

MALATTIE LINFOPROLIFERATIVE

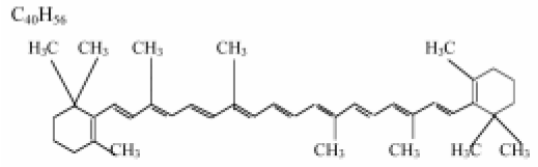
Introduzione

Questa definizione comprende la Vitamina A (o retinolo), i suoi derivati, come il retinene (o retinale) e l'acido retinoico, i carotenoidi e le provitamine A. I retinoidi sono composti labili e facilmente ossidabili. Per stabilizzarli e preservarne integra l'attività, i retinoidi nel composto vitaminico MDB sono solubilizzati in Vitamina E, che appunto li stabilizza e ne preserva le proprietà farmacologiche e terapeutiche.

In sintesi il razionale della MDB relativamente ai retinoidi e alle loro indicazioni nelle patologie neoplastiche poggiano su questi dati acquisiti e consolidati:

- Attività antiossidante, citostatica e di prevenzione dello sviluppo tumorale.
- Inibizione della mutagenesi.
- Attività antiproliferativa, pro-differenziante e pro-apoptotica sulle cellule tumorali.
- Inibizione dell'angiogenesi in tessuti tumorali.
- Azione antimetastatica, attraverso l'azione sull'adesività intercellulare e l'inibizione del passaggio delle cellule attraverso le barriere naturali di contenimento dell'invasività metastatica.
- Incremento del trofismo cellulare, particolarmente esaltato a livello degli epiteli, dell'immunità naturale e della risposta delle cellule Natural Killer.

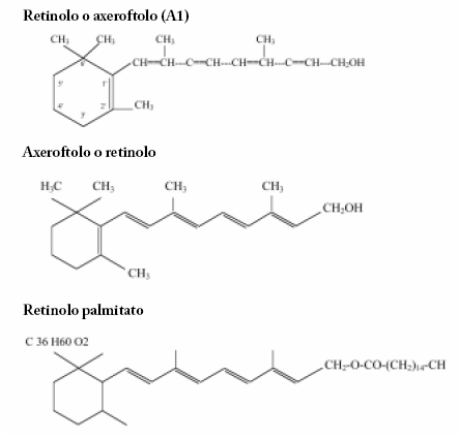
Betacarotene



β-carotene; *trans*-β-carotene;
(*all*-E)-1,1'-(3,7,12,16-tetramethyl-1,3,5,7,9,11,13,15,17-octocanonaene-1,18-dyl9bis[2,6,6,-trimethylcyclohexene]; E160a.

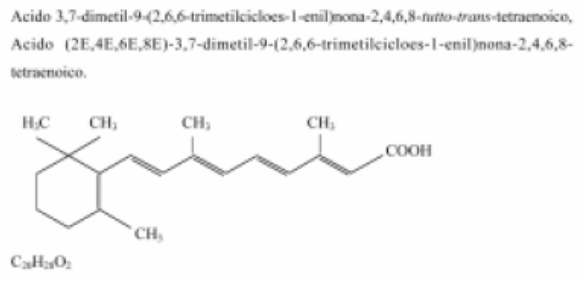
Il Prof. Luigi Di Bella ha inserito il betacarotene nel suo composto plurivitaminico sia per il notevole effetto di potenziamento ed esaltazione dell'azione degli altri componenti, che per il suo effetto protettivo su di essi e sulle membrane cellulari. I carotenoidi possono esercitare il loro effetto anti-tumorale senza essere convertiti nei loro metaboliti, il retinolo o l'acido retinico (Onogi, Okuno et al. 1998; Bertram and Vine 2005). Quindi il simultaneo trattamento con betacarotene e retinoidi può risultare in una più efficace azione antitumorale.

Vitamina A



Anche l'impiego della Vitamina A nella prevenzione e nel trattamento dei tumori, iniziato oltre 30 anni fa dal Prof. Di Bella, è documentato da numerose pubblicazioni nella letteratura scientifica (Mettlin 1984; Lippman and Meyskens 1988; Kelloff, Boone et al. 1996; Piedrafita and Pfahl 1997).

Acido retinoico tutto-trans (ATRA)



È derivato della Vitamina A per sostituzione del gruppo alcolico -OH col gruppo carbossilico -COOH. Da quasi 30 anni fa parte integrante del protocollo antitumorale del Prof. Di Bella (MDB) mentre da qualche anno è stato "scoperto" dalla ricerca medico scientifica ed è oggetto di una serie particolarmente vasta e crescente di studi sia clinici sia sperimentali (Okuno, Kojima et al. 2004; Soprano, Qin et al. 2004), che ne hanno confermato, come per gli altri componenti del MDB, la piena valenza sia preventiva che terapeutica nelle neoplasie.

In sintesi alcune delle azioni antineoplastiche dell'ATRA:

- Induce remissione nella leucemia acuta promielocitica (Avvisati and Tallman 2003; Pitha-Rowe, Petty et al. 2003; Sanz, Martin et al. 2003; Tallman 2004).
- Inibisce l'angiogenesi tumorale (Oikawa, Hirotani et al. 1989; Majewski, Szmurlo et al. 1994; Pal, Iruela-Arispe et al. 2000; Adachi, Itoh et al. 2001; Igarashi, Abe et al. 2001; Kini, Peterson et al. 2001).
- Induce trascrizione p21WAF1 ed attivazione di caspasi-1 (Arany, Ember et al. 2003; Arany, Whitehead et al. 2003).
- Sinergizza l'effetto di Bcl-2, sia sull'arresto della crescita, che sull'espressione del gene p21 (Chou, Chen et al. 2000).
- Induce l'arresto del ciclo cellulare in G0/G1 (Wu, Chen et al. 2001).
- Causa nelle cellule neoplastiche cambiamenti morfologici e biochimici come il restringimento della membrana, la condensazione della cromatina e la rottura del DNA, caratteristiche tipiche delle cellule in corso di apoptosi (Lee, Han et al. 2000).
- Diminuisce il potenziale di proliferazione neoplastica e ha un ruolo importante nella differenziazione, apoptosi e adesione cellulare (Voigt, Hartmann et al. 2000; Baroni, Paoletti et al. 2003).
- Rende particolarmente sensibili a chemioterapici le cellule neoplastiche (Carystinos, Alaoui-Jamali et al. 2001).
- Induce differenziazione nelle cellule neoplastiche (Kim, Kim et al. 2000; Antony, Freysz et al. 2001).

I retinoidi nelle malattie linfoproliferative.

Diversi studi hanno riportato un effetto inibitorio dell'acido retinoico sulla crescita di cellule di linfoma sia di origine B che T, in vitro. L'acido retinoico inibisce sia la proliferazione basale delle cellule di linfoma, sia quella indotta da fattori microambientali (Findley, Steuber et al. 1984; Turley, Funakoshi et al. 1995; Bonnefoix, Gressin et al. 1997; Niitsu, Higashihara et al. 2002; Guidoboni, Zancai et al. 2005).

È stato mostrato che la somministrazione di beta-carotene significativamente riduce l'incidenza di neoplasie linfoidi nei topi (Riondel, Wong et al. 2002). Inoltre, il beta-carotene, l'ATRA e l'acido 13-cis-retinoico prolungano la sopravvivenza di topi con linfomi murini trapiantati (Dillehay, Shealy et al. 1989; Ghosh, Mandal et al. 1995; Ghosh, Sardar et al. 1995; Basu, Banerjee et al. 2000). È stato riportato anche un ruolo protettivo dell'acido 13-cis-retinoico nell'induzione del linfoma timico nei topi (Przybyszewska 1985; Przybyszewska, Szaniawska et al. 1986).

I retinoidi (ATRA, acido 13-cis-retinoico ed analoghi sintetici come l'isotretinoin) sono stati usati per anni come monoterapia e/o in combinazione (per esempio con interferone alfa), per il trattamento del linfoma a cellule T cutaneo (micosi fungoide); il bexarotene, un retinoide sintetico altamente selettivo per il recettore-X-retinoide, ha attività contro le manifestazioni cutanee di tutte le fasi del linfoma a cellule T cutaneo (Kessler, Meyskens et al. 1983; Warrell, Coonley et al. 1983; Kessler, Jones et al. 1987; Neely, Mehlmauer et al. 1987; Serri, De Simone et al. 1990; Chow, Cheng et al. 1991; Knobler, Trautinger et al. 1991; Baranowitz 1994; Cheng, Su et al. 1994; Thomsen 1995; Chou, Su et al. 1996; Chen, Chang et al. 1998; Burg and Dummer 2000; Heald 2000; Kempf, Kettelhack et al. 2003; Zhang and Duvic 2003; Querfeld, Rosen et al. 2004).

L'uso di retinoidi sembra essere efficace anche nel trattamento di linfomi a cellule T periferici ricorrenti o refrattari. I meccanismi d'azione sono relativi all'induzione di differenziamento ed apoptosi nelle cellule di linfoma (Cheng, Su et al. 1994; Wang, Cheng et al. 2000; Huang, Lin et al. 2002).

È stato riportato anche il caso di un linfoma a cellule T associato al virus di Epstein-Barr, recidivato subito dopo chemioterapia e radioterapia, che è regredito dopo trattamento con acido 13-cis-retinoico (Su, Cheng et al. 1993).

Uno studio clinico ha valutato che in pazienti con linfoma non-Hodgkin refrattario o recidivato il trattamento con acido 9-cis retinoico ha solo una modesta attività (Younes, Cristofanilli et al. 2000).

L'associazione dei retinoidi con somatostatina, bromocriptina, melatonina, ciclofosfamide e ACTH è risultata essere molto efficace nel trattamento di pazienti con linfoma non-Hodgkin di basso grado in fase avanzata (Todisco, Casaccia et al. 2001). Ciò dimostra una migliore efficacia clinica dei retinoidi in associazione con molecole componenti il Metodo Di Bella, rispetto all'utilizzo dei retinoidi come singoli agenti antitumorali.

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Planta Med. 1995 Aug;61(4):317-20.

Physiological potential of beta-carotene in prolonging the survival of the host bearing transplantable murine lymphoma.

Ghosh B, Mandal A, Chatterjee M.

beta-Carotene, when supplemented in diet, has been found to increase the survival period of mice bearing a transplantable tumor, Dalton's lymphoma. Tumor cell-count, body weight pattern, hematological parameters like total count showed marked alterations in a dose-responsive manner with beta-carotene administration when compared to their untreated counterparts. Decreased tumor cell proliferation is also reflected by increased hemoglobin levels of the host.

Cancer Lett. 1995 Apr 14;90(2):191-7.

Role of beta-carotene on the changes in activity patterns and levels of biotransforming enzymes in transplantable murine lymphoma.

Ghosh B, Sardar S, Roy K, Chatterjee M.

The differential levels of induction of hepatic microsomal cytochrome P-450 (cyt. P-450), UDP-glucuronyl transferase (UDPGT) and cytosolic glutathione-S-transferase (GST) activities were evaluated over various periods of time, following tumor transplantation in male Swiss albino mice in the presence and absence of beta-carotene supplementation in their basal diet (100 mg/kg). An increase in the total hepatic microsomal cytochrome P-450 and UDP-glucuronyl transferase and cytosolic GSH-transferase activities (1.5 to 2 fold) occurred during the later stage of tumor progression (22 +/- 2 days onwards). However, beta-carotene supplementation throughout the study increased or decreased the random activity trends of the above markers significantly ($P < 0.05$- < 0.01). Finally, beta-carotene supplementation could enhance the survival of the host bearing lymphoma by almost 2-fold (50-60 days) over and above the lymphoma controls (30-35 days).

Cancer Res. 2005 Jan 15;65(2):587-95.

Retinoic acid inhibits the proliferative response induced by CD40 activation and interleukin-4 in mantle cell lymphoma.

Guidoboni M, Zancai P, Cariati R, Rizzo S, Dal Col J, Pavan A, Gloghini A, Spina M, Cuneo A, Pomponi F, Bononi A, Doglioni C, Maestro R, Carbone A, Boiocchi M, Dolcetti R.

Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin's lymphoma with poor response to therapy and unfavorable prognosis. Here, we show that retinoic acid (RA) isomers significantly inhibit the proliferation of both primary MCL cultures (n = 7) and established cell lines (Granta 519 and SP-53) as shown by [(3)H]thymidine uptake and carboxyfluorescein diacetate succinimidyl ester labeling coupled with cyclin D1 staining. RA induces cell accumulation in G(0)-G(1) together with a marked up-regulation of p27(Kip1) by inhibiting ubiquitination and proteasome-dependent degradation of the protein. The p21(Cip1) inhibitor was also up-regulated by RA in Granta 519 cells, whereas the expression of cyclin D1 is unaffected. Most of RA-induced p27(Kip1) was bound to cyclin D1/cyclin-dependent kinase 4 complexes, probably contributing to the decreased cyclin-dependent kinase 4 kinase activity and pRb hypophosphorylation observed in RA-treated cells. Experiments with receptor-selective ligands indicate that RA receptor alpha cooperates with retinoid X receptors in mediating RA-dependent MCL cell growth inhibition. Notably, RA isomers, and particularly 9-cis-RA, also inhibited the growth-promoting effect induced in primary MCL cells by CD40 activation alone or in combination with interleukin-4. Immunohistochemical analysis showed that significant numbers of CD40L-expressing lymphoid cells are present in lymph node biopsies of MCL patients. These results therefore further strengthen the possibility that triggering of CD40 by infiltrating CD40L+ cells may continuously promote the growth of MCL cells in vivo. On these grounds, our findings that RA inhibits basal MCL proliferation as well as MCL growth-promoting effects exerted by microenvironmental factors make these compounds highly attractive in terms of potential clinical efficacy in this setting.

Clin Lymphoma. 2000 Nov;1 Suppl 1:S45-9.

The treatment of cutaneous T-cell lymphoma with a novel retinoid.

Heald P.

The clinical experience with bexarotene for cutaneous T-cell lymphoma (CTCL) at our center is reviewed here. Disease activity assessment was monitored every 4 weeks in all patients. Five target lesions were monitored, an area score was performed, and a CTCL-specific health assessment questionnaire was administered. Four patients with refractory plaque CTCL were treated with bexarotene gel. All target lesions disappeared after 8 weeks of therapy, with recurrences observed in untreated areas. In the follow-up period, no recurrences of the original target lesions were observed. One patient withdrew from the study. Patients with refractory patch/plaque disease were randomized to a high-dose (300 mg/m(2)) or low-dose (6.5 mg/m(2)) daily oral regimen of bexarotene. After showing disease progression, the two patients on the low-dose arm were entered into the high-dose arm after 8 weeks. Marked clinical responses were seen in all patients treated. The target lesions showed either complete disappearance or a reduction in lesion size, duration, and scale. No new lesions were noted in patients on high-dose bexarotene. Self-assessments also confirmed the palliative properties of the observed responses. All patients had hypertriglyceridemia despite the concomitant administration of atorvastatin at 60 mg/day. Dose reductions were required to maintain safe lipid levels. Four patients with erythrodermic CTCL were treated with high-dose oral therapy, and all patients showed rapid (within 2 weeks) improvement of erythroderma and symptoms.

Leuk Lymphoma. 2002 Jul;43(7):1415-20.

Combination of 13-cis retinoic acid and interferon-alpha in the treatment of recurrent or refractory peripheral T-cell lymphoma.

Huang CL, Lin ZZ, Su IJ, Chao TY, Tien HF, Chang MC, Huang MC, Kao WY, Tang JL, Yeh KH, Wang CH, Hsu CH, Liu MY, Cheng AL.

We previously reported the therapeutic efficacy of 13-cis retinoic acid (13-cRA) in some subtypes of peripheral T-cell lymphoma (PTCL). This study sought to clarify if the addition of interferon-alpha2a (IFN-alpha2a), an agent with synergistic cytotoxicity with 13-cRA in many types of malignant cells, may be more effective in the treatment of PTCL. Eligible patients has histologically proven PTCL, which was recurrent after or refractory to anthracycline-containing systemic chemotherapy. The treatment included oral administration of 13-cRA 1 mg/kg/day, divided into three doses, and intramuscular injection of IFN-alpha2a 4.5 MU/M2, three times per week. From March 1995 to July 2000, a total of 17 patients, 10 men and 7 women, with a median age of 47 years (range, 18-77 years), were recruited. The histologic diagnosis included 7 cases of unspecified PTCL, 6 cases of Ki-1 anaplastic large cell lymphoma (ALCL), 1 case of angioimmunoblastic T-cell lymphoma, and 3 cases of angiocentric nasal NK/T cell lymphoma. They received a median of 1.7 months of treatment (range, 0.4-13.3 months). One patient refused further treatment due to toxicity. The doses of 13-cRA and IFN-alpha2a had to be decreased in 7 and 7 patients, respectively. Grade III/IV hematologic and non-hematologic toxicity developed in 2 and 5 patients, respectively. There were 5 partial responses (Ki-1, 4; unspecified PTCL, 1), with a total response rate of 31.3% (95% CI, 5.7-56.8%). The median duration of response for the responders was 2.5 months (range, 0.8-7.2 months). The median overall survival for the entire group of patients was 3.6 months. In conclusion, a combination of 13-cRA and IFN-alpha2a is a useful salvage treatment for selected patients with recurrent or refractory PTCL, particularly those with the Ki-1 subtype. However, the data does not support that addition of IFN-alpha2a is superior to 13-cRA alone.

Tohoku J Exp Med. 2001 May;194(1):35-43.

Retinoic acids repress the expression of ETS-1 in endothelial cells.

Igarashi T, Abe M, Oikawa M, Nukiwa T, Sato Y.

The transcription factor ETS-1 expressed in endothelial cells (ECs) regulates angiogenesis by inducing MMP-1, MMP-3, MMP-9, u-PA and integrin beta3 in endothelial cells (ECs). Here, we examined whether antiangiogenic retinoic acids affect the expression of ETS-1 in ECs. The expression of ets-1 mRNA was up-regulated in sparse to subconfluent ECs and down-regulated in confluent ECs. When confluent ECs were stimulated with basic fibroblast growth factor (bFGF), ets-1 mRNA was induced. All-trans retinoic acid (ATRA) as well as 9-cis retinoic acid reduced the augmented expression of ets-1 mRNA in both subconfluent ECs and bFGF-treated confluent ECs. This inhibitory effect of ATRA was dose dependent and was evident at a concentration as low as 10(-7) M. ATRA did not alter the stability of ets-1 mRNA. Moreover, promoter analysis indicated that ATRA repressed the expression of ets-1 mRNA at transcriptional level. As a result, ATRA reduced the binding of ETS-1 protein to the ETS binding motif. These results indicate that the anti-angiogenic effect of retinoic acids is mediated at least in part by the transcriptional repression of ets-1 mRNA in ECs.

J Cell Biochem Suppl. 1996;26:1-28.

New agents for cancer chemoprevention.

Kelloff GJ, Boone CW, Crowell JA, Steele VE, Lubet RA, Doody LA, Malone WF, Hawk ET, Sigman CC.

Clinical chemoprevention trials of more than 30 agents and agent combinations are now in progress or being planned. The most advanced agents are well known and are in large Phase III chemoprevention intervention trials or epidemiological studies. These drugs include several retinoids [e.g., retinol, retinyl palmitate, all-trans-retinoic acid, and 13-cis-retinoic acid], calcium, Beta carotene, vitamin E, tamoxifen, and finasteride. Other newer agents are currently being evaluated in or being considered for Phase II and early Phase III chemoprevention trials. Prominent in this group are all-trans-N-(4-hydroxy phenyl)retinamide (4-HPR) (alone and in combination with tamoxifen), 2-difluoromethylornithine (DFMO), nonsteroidal antiinflammatory drugs (aspirin, piroxicam, sulindac), oltipraz, and dehydroepiandrostenedione (DHEA). A third group is new agents showing chemopreventive activity in animal models, epidemiological studies, or in pilot clinical intervention studies. They are now in preclinical toxicology testing or Phase I safety and pharmacokinetics trials preparatory to chemoprevention efficacy trials. These agents include S-allyl-l-cysteine, curcumin, DHEA analog 8354 (fluasterone), genistein, ibuprofen, indole-3-carbinol, perillyl alcohol, phenethyl isothiocyanate, 9-cis-retinoic acid, sulindac sulfone, tea extracts, ursodiol, vitamin D analogs, and p-xylyl selenocyanate. A new generation of agents and agent combinations will soon enter clinical chemoprevention studies based primarily on promising chemopreventive activity in animal models and in mechanistic studies. Among these agents are more efficacious analogs of known chemopreventive drugs including novel carotenoids (e.g., alpha-carotene and lutein). Also included are safer analogs which retain the chemopreventive efficacy of the parent drug such as vitamin D3 analogs. Other agents of high interest are aromatase inhibitors (e.g., (+)-vorozole), and protease inhibitors (e.g., Bowman-Birk soybean trypsin inhibitor). Combinations are also being considered, such as vitamin E with l-selenomethionine. Analysis of signal transduction pathways is beginning to yield classes of potentially active and selective chemopreventive drugs. Examples are ras isoprenylation and epidermal growth factor receptor inhibitors.

Hematol Oncol Clin North Am. 2003 Dec;17(6):1405-19.

Topical and systemic retinoid therapy for cutaneous T-cell lymphoma.

Kempf W, Kettelhack N, Duvic M, Burg G.

Because curative therapies for CTCL are not yet available, short of TSEB in patients who have early-stage disease and allogeneic bone marrow transplantation in patients who have more advanced disease, the goal of current therapies is to prevent progression of MF and to preserve quality of life. The overall conclusion drawn from the studies reported in the literature, is that retinoids as monotherapy, or in combination with other nonaggressive treatment modalities, represent a low-risk treatment alternative that is especially suitable for controlling early stages of MF and other CTCL. A combination of therapies may be more effective in controlling CTCL as shown with IFN-alpha plus retinoids, and, recently, IFN-alpha with bexarotene and other modalities. For example, isotretinoin, followed by TSEB (for stage I to II disease) or preceded by chemotherapy (for stage II and IV disease) and bexarotene plus PUVA or photopheresis plus IFN, gave overall response rates of 82% and 69% in patients who had MF and SS, respectively. Retinoids as monotherapy may induce complete remissions, but usually these responses are of short duration and relapses are common. Clinical response is not identical to histologic clearance. Even in cases with clinically complete clearance of skin lesions, lymphoid infiltrates persisted, which are most likely the source of recurrences. The new generation of retinoids, the RXR selective agonists like bexarotene, represent a promising approach for refractory or persistent MF that is unresponsive to first-line therapies. Individual differences in response to retinoids may be due to different expression of retinoid receptors, functional polymorphisms in metabolizing retinoids, or resistance to some retinoids. In the future, pharmacogenomic studies are needed to clarify the mechanisms that underlie the differing response rates of patients who have CTCL to retinoids. In addition, new agonists of RAR and RXR, either selective or pan agonists, will become available and will enlarge the spectrum of vitamin A analogs that have antitumoral properties.

Arch Dermatol. 1987 Feb;123(2):201-4.

Isotretinoin and cutaneous helper T-cell lymphoma (mycosis fungoides).

Kessler JF, Jones SE, Levine N, Lynch PJ, Booth AR, Meyskens FL Jr.

Retinoids, including isotretinoin, have demonstrated antiproliferative and antineoplastic activity in laboratory and clinical trials. In a phase II trial, 25 patients with extensive mycosis fungoides were evaluated for response to isotretinoin. There was a 44% (11 patients) objective clinical response rate with three clinical complete responses without concomitant evidence of pathologic clearing of the disease. An additional 24% (six patients) showed a minor degree of clinical improvement. The median time to response was two months (range, 0.5 to eight months) and the median response duration was eight months or longer (range, one to 25 months). Chronic toxic reactions consisted primarily of drying of the skin and mucous membranes and resulted in dose reduction in the majority of patients. It is concluded that isotretinoin produces significant clinical benefit to some patients with mycosis fungoides.

Lancet. 1983 Jun 18;1(8338):1345-7.

Treatment of cutaneous T-cell lymphoma (mycosis fungoides) with 13-cis-retinoic acid.

Kessler JF, Meyskens FL Jr, Levine N, Lynch PJ, Jones SE.

Four patients with refractory cutaneous T-cell lymphoma (mycosis fungoides) were treated with 13-cis-retinoic acid. Near complete clearing of extensive tumours and plaques was seen in one patient, who remains in partial remission with continued improvement after fifteen months. Two patients showed improvement in pruritus and 50% reduction in plaques by four and six weeks, respectively. The fourth patient had improvement in pruritus and clearing of plaques, but dryness and scaling necessitated reduction and eventually withdrawal of the treatment.

J Cell Physiol. 2000 Mar;182(3):421-8.

Participation of type II protein kinase A in the retinoic acid-induced growth inhibition of SH-SY5Y human neuroblastoma cells.

Kim SN, Kim SG, Park SD, Cho-Chung YS, Hong SH.

To examine the role of protein kinase A (EC 2.7.1.37) isozymes in the retinoic acid-induced growth inhibition and neuronal differentiation, we investigated the changes of protein kinase A isozyme patterns in retinoic acid-treated SH-SY5Y human neuroblastoma cells. Retinoic acid induced growth inhibition and neuronal differentiation of SH-SY5Y cells in a dose- and time-dependent manner. Neuronal differentiation was evidenced by extensive neurite outgrowth, decrease of N-Myc oncoprotein, and increase of GAP-43 mRNA. Type II protein kinase A activity increased by 1.5-fold in differentiated SH-SY5Y cells by retinoic acid treatment. The increase of type II protein kinase A was due to the increase of RIIbeta and Calpha subunits. Since type II protein kinase A and RIIbeta have been known to play important role(s) in the growth inhibition and differentiation of cancer cells, we further investigated the role of the increased type II protein kinase A by overexpressing RIIbeta in SH-SY5Y cells. The growth of RIIbeta-overexpressing cells was slower than that of parental cells, being comparable to that of retinoic acid-treated cells. Retinoic acid treatment further increased the RIIbeta level and further inhibited the growth of RIIbeta-overexpressing cells, showing strong correlation between the level of RIIbeta and growth inhibition. However, RIIbeta-overexpressing cells did not show any sign of neuronal differentiation and responded to retinoic acid in the same way as parental cells. These data suggest that protein kinase A participates in the retinoic acid-induced growth inhibition through the up-regulation of RIIbeta/type II protein kinase A.

Blood. 2001 Jun 15;97(12):3919-24.

Angiogenesis in acute promyelocytic leukemia: induction by vascular endothelial growth factor and inhibition by all-trans retinoic acid.

Kini AR, Peterson LA, Tallman MS, Lingen MW.

Recent studies indicate that angiogenesis is important in the pathogenesis of leukemias, apart from its well-established role in solid tumors. In this study, the possible role of angiogenesis in acute promyelocytic leukemia (APL) was explored. Bone marrow trephine biopsies from patients with APL showed significantly increased microvessel density and hot spot density compared with normal control bone marrow biopsies. To identify the mediators of angiogenesis in APL, quantitative and functional assays were performed using the NB4 APL cell line as a model system. Conditioned media (CM) from the NB4 cells strongly stimulated endothelial cell migration. CM from the NB4 cells contained high levels of vascular endothelial growth factor (VEGF) but not basic fibroblast growth factor (bFGF). Most important, the addition of neutralizing VEGF antibodies completely inhibited the ability of NB4 CM to stimulate endothelial cell migration, suggesting that APL angiogenesis is mediated by VEGF. The effect of all-trans retinoic acid (ATRA) on APL angiogenesis was then studied. ATRA therapy resulted in a decrease in bone marrow microvessel density and hot spot density. CM from ATRA-treated APL cells did not stimulate endothelial cell migration. Finally, quantitative assays showed that ATRA treatment resulted in the abrogation of VEGF production by the NB4 cells. These results show that there is increased angiogenesis and VEGF production in APL and that ATRA therapy inhibits VEGF production and suppresses angiogenesis. The addition of specific antiangiogenic agents to differentiation therapy or chemotherapy should be explored.

J Am Acad Dermatol. 1991 Feb;24(2 Pt 1):247-52.

Treatment of cutaneous T cell lymphoma with a combination of low-dose interferon alfa-2b and retinoids.

Knobler RM, Trautinger F, Radaszkiewicz T, Kokoschka EM, Micksche M.

In a pilot study the therapeutic effect and side effect profile of low-dose interferon alfa-2b in combination with a retinoid for the treatment of cutaneous T cell lymphoma were evaluated. Seven patients (four women, three men) with histologically confirmed cutaneous T cell lymphoma were included. Four patients had received therapy previously. The treatment schedule consisted of 2 million U of interferon alfa-2b administered subcutaneously three times per week and oral 13-cis-retinoic acid, 1 mg/kg/day, with subsequent dose reduction in case of response. The combination therapy produced two complete and two partial remissions. Responses were maintained by continuous therapy for up to 15 months even after dose reduction of both agents by 50%. Side effects were negligible and did not result in discontinuation of treatment in any patient.

Biochem Pharmacol. 2000 Mar 1;59(5):485-96.

Differential effects of retinoic acid on growth and apoptosis in human colon cancer cell lines associated with the induction of retinoic acid receptor beta.

Lee MO, Han SY, Jiang S, Park JH, Kim SJ.

Retinoids are well known as potential chemopreventive and chemotherapeutic agents against a variety of human cancers. Here, we report that retinoic acid (RA) induced differential growth inhibition in human colon cancer cell lines: while DLD-1, HT-29, and WiDr were relatively resistant, HCT-15 and Colo201 were relatively sensitive. All-trans-retinoic acid caused morphological and biochemical changes such as membrane shrinkage, chromatin condensation, and DNA cleavage, which are typical features of cells undergoing apoptosis in sensitive cell lines. Although retinoic acid receptor (RAR)alpha, beta, gamma and retinoid X receptor alpha were expressed in all cell lines examined, a significant induction of RARbeta by all-trans-RA was observed only in sensitive cell lines, suggesting important roles of RARbeta in RA sensitivity. When a vector containing the RARbeta gene was introduced into a relatively resistant cell line, DLD-1, the cells acquired RA sensitivity. Further, we found that the RARbeta transfectants of DLD-1 expressed an enhanced level of c-Myc and Bax proteins, which may result in the increased susceptibility of the cells to all-trans-RA-induced apoptosis. In summary, our data demonstrated that RA induced growth inhibition and apoptosis in human colon cancer cells and that the induction of RAR3 may mediate the retinoid action.

J Am Coll Nutr. 1988 Aug;7(4):269-84.

Vitamin A derivatives in the prevention and treatment of human cancer.

Lippman SM, Meyskens FL Jr.

Vitamin A is essential for normal cellular growth and differentiation. A vast amount of laboratory data have clearly demonstrated the potent antiproliferative and differentiation-inducing effects of vitamin A and the synthetic analogues (retinoids). Recent in-vitro work has led to the exciting proposal that protein kinase-C may be centrally involved in many of retinoids' anticancer actions including the effects on ornithine decarboxylase induction, intracellular polyamine levels, and epidermal growth factor receptor number. Several intervention trials have clearly indicated that natural vitamin A at clinically tolerable doses has only limited activity against human neoplastic processes. Therefore, clinical work has focused on the synthetic derivatives with higher therapeutic indexes. In human cancer prevention, retinoids have been most effective for skin diseases, including actinic keratosis, keratoacanthoma, epidermodysplasia verruciformis, dysplastic nevus syndrome, and basal cell carcinoma. Several noncutaneous premaligancies, however, are currently receiving more attention in retinoid trials. Definite retinoid activity has been documented in oral leukoplakia, laryngeal papillomatosis, superficial bladder carcinoma, cervical dysplasia, bronchial metaplasia, and preleukemia. Significant therapeutic advances are also occurring with this class of drugs in some drug-resistant malignancies and several others that have become refractory, including advanced basal cell cancer, mycosis fungoides, melanoma, acute promyelocytic leukemia, and squamous cell carcinoma of the skin and of the head and neck. This report comprehensively presents the clinical data using retinoids as anticancer agents in human premalignant disorders and outlines the ongoing and planned studies with retinoids in combination and adjuvant therapy.

Int J Cancer. 1994 Apr 1;57(1):81-5.

Synergistic effect of retinoids and interferon alpha on tumor-induced angiogenesis: anti-angiogenic effect on HPV-harboring tumor-cell lines.

Majewski S, Szmurlo A, Marczak M, Jablonska S, Bollag W.

Various retinoids and interferons exert anti-tumor effects both in experimental studies and in clinical trials. Recent reports indicate that they have a synergistic antineoplastic activity. Our study aimed to determine whether these synergistic anti-tumor effects are related to inhibition of tumor-cell-induced angiogenesis. A further aim was to compare the anti-angiogenic activity of various retinoids including 9-cis retinoic acid, a ligand for nuclear retinoic acid receptor RXR, given alone and in combination with interferon alpha-2a (IFN alpha-2a). An in vivo experimental model of cutaneous angiogenesis in the mouse was used. Angiogenesis was induced by intradermal injection of HPV16- or HPV18 DNA-harboring tumor-cell lines. All-trans retinoic acid (all-trans RA), 13-cis retinoic acid (13-cis RA) and 9-cis retinoic acid (9-cis RA) as well as IFN alpha-2a applied to mice intraperitoneally for 5 consecutive days before induction of angiogenesis resulted in significant inhibition of angiogenesis. Combination of retinoids with IFN alpha-2a led to a synergistic inhibition of angiogenesis, as compared to the effects of the drugs given alone. Similar results were obtained when tumor cells were preincubated in vitro with the compounds, before injection into untreated mice. Our findings on synergistic anti-angiogenic effects of retinoids and IFN alpha-2a could explain, at least partially, the anti-tumor efficacy of combined therapy with these agents, and provide support for the role of angiogenesis in tumor growth.

Adv Nutr Res. 1984;6:47-65.

Epidemiologic studies on vitamin A and cancer.

Mettlin C.

Data derived from epidemiologic studies on human populations are consistent with the protection from cancer afforded by vitamin A seen in animal studies. The populations studied are diverse, including groups living in India, Singapore, Norway, the United Kingdom, and the United States. The methodologies brought to bear on the question have been equally varied. Although there are inconsistencies in findings, and instances in which an association has not been observed, the weight of evidence suggests that the intake of vitamin A from dietary or other sources may inhibit the onset of lung cancer and possibly other cancers. However, the evidence from human populations is not experimental and it is conceivable that the associations observed are not causal. Additional epidemiologic research is needed to determine what sites of cancer may be inhibited by vitamin A and whether cancer growth at any other site is enhanced by high vitamin A intakes. It is also important that controlled trials using vitamin A as a chemopreventive agent be considered as a means of determining whether the epidemiologic findings are of clinical significance.

Arch Intern Med. 1987 Mar;147(3):529-31.

The effect of isotretinoin in six patients with cutaneous T-cell lymphoma.

Neely SM, Mehlmauer M, Feinstein DI.

Oral retinoids are effective in the treatment of patients with a variety of malignant and nonmalignant skin disorders, including mycosis fungoides. We treated six patients with cutaneous T-cell lymphomas with isotretinoin 1 to 2 mg/kg/d. All patients experienced symptomatic relief (fading of skin lesions and disappearance of pruritus) within two to eight weeks of starting the drug therapy; pretreatment and posttreatment biopsy specimens were unchanged. Adverse effects were minor and primarily consisted of drying of the mucous membranes. We conclude that isotretinoin is a well-tolerated, easily administered drug that provides good palliation of symptoms and signs associated with cutaneous T-cell lymphoma in patients who are unable or unwilling to comply with standard therapy.

Leuk Res. 2002 Aug;26(8):745-55.

Human B-cell lymphoma cell lines are highly sensitive to apoptosis induced by all-trans retinoic acid and interferon-gamma.

Niitsu N, Higashihara M, Honma Y.

When cells were incubated in the presence of both interferon-gamma (IFN-gamma) and all-trans retinoic acid (ATRA), the concentration of IFN-gamma required to induce apoptosis of B-cell lymphoma cells was much lower than that required for myeloid or erythroid cell lines. The concentration of IFN-gamma that effectively inhibited the proliferation of BALM-3 cells was 1/40 of that required for BALM-1 cells. STAT-1 phosphorylation, IRF-1 mRNA and protein expression and RAR-beta expression were enhanced to a greater degree in BALM-3 cells treated with IFN-gamma and ATRA than in BALM-1 cells treated with IFN-gamma and ATRA, suggesting that these IFN-gamma related genes were involved in the induction of apoptosis of BALM-3 cells.

Cancer Lett. 1989 Nov 30;48(2):157-62.

A highly potent antiangiogenic activity of retinoids.

Oikawa T, Hirotani K, Nakamura O, Shudo K, Hiragun A, Iwaguchi T.

Four retinoids, i.e. retinol (vitamin A), retinoic acid, retinyl acetate and synthetic chalcone carboxylic acid (Ch 55), were examined for their effects on embryonic angiogenesis using 4.5-day chorioallantoic membranes of chick embryo. The effects of these retinoids were compared with that of antibiotic herbimycin A, which was the most powerful inhibitor of the angiogenesis reported previously. The four retinoids strongly inhibited embryonic angiogenesis; the order of inhibitory activity was Ch 55 greater than retinoic acid greater than herbimycin A greater than retinyl acetate based on the dose required for the half-maximal inhibitory effect. The present results suggest that retinoids are effective inhibitors of angiogenesis, and can be applied for the management of certain diseases accompanied by aberrant angiogenesis, particularly that which occurs during progressive growth of solid tumors.

Curr Cancer Drug Targets. 2004 May;4(3):285-98.

Retinoids in cancer chemoprevention.

Okuno M, Kojima S, Matsushima-Nishiwaki R, Tsurumi H, Muto Y, Friedman SL, Moriwaki H.

We review the therapeutic and preventive applications of a retinoid analog (vitamin A and its derivatives) for human cancers. Chemoprevention of cancer is an intervention in the carcinogenic process by chemical agents that block or reverse the malignant transformation of cells. Retinoids are prime candidates for cancer chemoprevention since cancer is characterized by abnormal growth with a lack of differentiation, which could be modified by retinoids. Retinoids exert their biological functions through nuclear receptors, retinoic acid receptor (RAR) and retinoid X receptor (RXR). A number of experimental and clinical studies have been performed in the past two decades with retinoids showing that they inhibit or reverse the carcinogenic process in some organs, including hematological malignancy as well as premalignant and malignant lesions in the oral cavity, head and neck, breast, skin and liver. We particularly focus upon the therapeutic application of all-trans RA (atRA) to acute promyelocytic leukemia (APL) and on the preventive approach to hepatocellular carcinoma (HCC) by a synthetic retinoid analog, acyclic retinoid. In both malignancies, malfunction of retinoid nuclear receptors is closely related to their carcinogenic process. In APL, a chromosomal translocation produces a chimeric protein between RAR alpha and a protein called promyelocyte leukemia protein (PML). PML-RAR alpha works as a dominant negative receptor in the leukemic cells, interfering with the normal function of RAR alpha and/or PML, which in turn results in the arrest of cell maturation at the stage of promyelocytes. Oral administration of atRA induces differentiation of promyelocytic leukemic cells to mature neutrophils, and leads to a high rates (over 90%) of complete remission. AtRA therapy has become standard in the treatment of APL. In the case of HCC, post-translational modification of RXR by phosphorylation impairs its function, which leads to uncontrolled cell growth. Acyclic retinoid suppresses the phosphorylation of RXR alpha, restores its function in the presence of its endogenous ligand, 9-cis RA, and thereby induces apoptosis of the cancer cells. Acyclic retinoid given orally successfully suppresses the development of second primary tumors in cirrhotic patients who undergo curative removal of preceding HCC. Eradication of (pre)malignant clones ('clonal deletion') from the liver is suggested as a mechanism of the chemopreventive effect. Further development of more effective retinoids as well as their use in combination with other classes of anticancer agents including immunopreventive drugs like interferons may provide strategies for cancer prevention.

Nutr Cancer. 1998;32(1):20-4.

Antiproliferative effect of carotenoids on human colon cancer cells without conversion to retinoic acid.

Onogi N, Okuno M, Matsushima-Nishiwaki R, Fukutomi Y, Moriwaki H, Muto Y, Kojima S.

The present study employed two human colon cancer cell lines, DLD-1 and Colo 320DM, to investigate whether the provitamin A activity of carotenoids is necessary for their antitumor effect on colon cancer. Carotenoids, including alpha- and beta-carotene and canthaxanthin, significantly suppressed cell viability [measured by tetrazolium (MTT) assay], DNA synthesis (measured by [3H]thymidine uptake), and cell proliferation (measured by cell counting) and thus showed growth-inhibitory effects on both cancer cell lines. Because canthaxanthin does not have provitamin A activity, these results suggest that the carotenoid directly inhibited the cell growth. Moreover, the effective dose of retinoic acid, an active metabolite of vitamin A, was much higher than that of alpha- or beta-carotene. A retinoic acid-inducible gene, retinoic acid receptor-beta, was not enhanced in either type of cancer cell by treatment with alpha- or beta-carotene. Therefore, like canthaxanthin, alpha- and beta-carotene might also exert their tumor-suppressing effects without being converted to retinoids. These results suggest that a certain antitumor activity of carotenoids may not necessarily require their provitamin A activity.

Microvasc Res. 2000 Sep;60(2):112-20.

Retinoic acid selectively inhibits the vascular permeabilizing effect of VPF/VEGF, an early step in the angiogenic cascade.

Pal S, Iruela-Arispe ML, Harvey VS, Zeng H, Nagy JA, Dvorak HF, Mukhopadhyay D.

All-trans-retinoic acid (RA) and other retinoids modulate cell growth and differentiation, generally favoring terminal cell differentiation and inhibiting carcinogenesis. Retinoids are also reported to inhibit angiogenesis and endothelial cell migration, actions that are also anti-carcinogenic. Vascular permeability factor/vascular endothelial growth factor (VPF/VEGF) is a multifunctional cytokine secreted by many tumors. It renders microvessels hyperpermeable to plasma and stimulates endothelial cell migration and division. To investigate further the mechanisms by which RA inhibits angiogenesis, we evaluated the effects of RA on VPF/VEGF-induced angiogenesis and microvascular permeability. RA selectively inhibited the angiogenic response induced by VPF/VEGF, but not that induced by fibroblast growth factor-2 (FGF-2), in the CAM assay. RA and two of its isomers also inhibited the vascular permeabilizing effect of VPF/VEGF but not that induced by histamine. The vascular permeabilization induced by VPF/VEGF and blocked by RA takes place within 1-15 min, too short a time frame for RA to act by modulating transcription through classic retinoid receptors. RA also inhibited VPF/VEGF-induced phosphorylation of PLC-gamma and synthesis of cGMP but actually increased VPF/VEGF binding to cultured endothelial cells. Taken together, these findings indicate that RA selectively blocks VPF/VEGF-induced microvascular permeability and angiogenesis and also identify VPF/VEGF as a major target of RA action. The selectivity of RA's action suggests that other, RA-independent pathways must exist for the angiogenesis induced by FGF-2 and the vascular permeabilizing effect of histamine.

Mol Cell Biol. 1997 Nov;17(11):6348-58.

Retinoid-induced apoptosis and Sp1 cleavage occur independently of transcription and require caspase activation.

Piedrafita FJ, Pfahl M.

Vitamin A and its derivatives, the retinoids, are essential regulators of many important biological functions, including cell growth and differentiation, development, homeostasis, and carcinogenesis. Natural retinoids such as all-trans retinoic acid can induce cell differentiation and inhibit growth of certain cancer cells. We recently identified a novel class of synthetic retinoids with strong anti-cancer cell activities in vitro and in vivo which can induce apoptosis in several cancer cell lines. Using an electrophoretic mobility shift assay, we analyzed the DNA binding activity of several transcription factors in T cells treated with apoptotic retinoids. We found that the DNA binding activity of the general transcription factor Sp1 is lost in retinoid-treated T cells undergoing apoptosis. A truncated Sp1 protein is detected by immunoblot analysis, and cytosolic protein extracts prepared from apoptotic cells contain a protease activity which specifically cleaves purified Sp1 in vitro. This proteolysis of Sp1 can be inhibited by N-ethylmaleimide and iodoacetamide, indicating that a cysteine protease mediates cleavage of Sp1. Furthermore, inhibition of Sp1 cleavage by ZVAD-fmk and ZDEVD-fmk suggests that caspases are directly involved in this event. In fact, caspases 2 and 3 are activated in T cells after treatment with apoptotic retinoids. The peptide inhibitors also blocked retinoid-induced apoptosis, as well as processing of caspases and proteolysis of Sp1 and poly(ADP-ribose) polymerase in intact cells. Degradation of Sp1 occurs early during apoptosis and is therefore likely to have profound effects on the basal transcription status of the cell. Interestingly, retinoid-induced apoptosis does not require de novo mRNA and protein synthesis, suggesting that a novel mechanism of retinoid signaling is involved, triggering cell death in a transcriptional activation-independent, caspase-dependent manner.

Leukemia. 2003 Sep;17(9):1723-30.

Retinoid target genes in acute promyelocytic leukemia.

Pitha-Rowe I, Petty WJ, Kitareewan S, Dmitrovsky E.

All-trans-retinoic acid (RA)-based differentiation therapy induces clinical remissions in acute promyelocytic leukemia (APL). This has propelled interest in elucidating the molecular mechanisms responsible for these remissions. The t(15;17) rearrangement results in the expression of the PML/RARalpha fusion transcript that is paradoxically linked to the etiology and clinical retinoid response in APL. PML/RARalpha expression blocks terminal myeloid differentiation in APL. Treatment with pharmacological RA dosages overcomes the dominant-negative effects of PML/RARalpha to activate transcription of retinoid target genes. This regulation is linked directly to RA effects in APL, including PML/RARalpha degradation and induction of differentiation. Identifying retinoid target genes is an important step in developing a mechanistic understanding of RA effects in APL. RA target genes have been uncovered through the use of molecular genetic approaches as well as unique cellular and transgenic APL models. Recent developments in the proteomic and functional genomic fields are providing useful tools for elucidating mechanisms of RA response or resistance in APL. These target genes represent potential therapeutic targets in APL and other retinoid-responsive diseases. Previous spotlights in Leukemia have highlighted the importance of cytokine effects and signal transduction crosstalk in retinoid response in APL and in normal hematopoiesis. This review builds on prior work by addressing the role of retinoid target genes in mediating retinoid response or resistance in APL.

Arch Immunol Ther Exp (Warsz). 1985;33(6):811-5.

A protective role of 13-cis retinoic acid in thymic lymphoma induction.

Przybyszewska M.

The aim of the study was to analyze the incidence of X-ray induced lymphomas in C57B1/10W mice kept on diet with varying retinoid content. The mice whose diet was supplemented with 13-cis retinoic acid (300 mg per kg of chow) developed less lymphomas than those kept on Vitamin A deficient diet as well as on a standard diet (15 mg per kg of chow). Mice subjected to Vitamin A deficient diet displayed a shortening of the latency period.

Neoplasma. 1986;33(3):341-4.

Effect of 13-cis-retinoic acid on the spontaneous thymic lymphoma development in AKR mice.

Przybyszewska M, Szaniawska B, Janik P.

The aim of the study was to analyze the incidence of spontaneous thymic lymphomas in AKR mice kept on a diet with normal and excess retinoid content. The mice whose diet was supplemented with 13-cis-retinoic acid (250 mg per kg chow) developed less lymphomas than those kept on a standard diet (15 mg per kg chow). The effect of cyclophosphamide on the early stage of lymphomogenesis was tested using a single dose (100 mg per kg body weight), injected intraperitoneally to AKR mice. Increased incidence of lymphoma following cyclophosphamide administration was observed as result of a) low sensitivity of prelymphoma and lymphoma cells and/or b) immunosuppressive effect of cyclophosphamide.

J Am Acad Dermatol. 2004 Jul;51(1):25-32.

Comparison of selective retinoic acid receptor- and retinoic X receptor-mediated efficacy, tolerance, and survival in cutaneous t-cell lymphoma.

Querfeld C, Rosen ST, Guitart J, Rademaker A, Fung BB, Posten W, Kuzel TM.

Primary cutaneous T-cell lymphomas are non-Hodgkin's lymphomas with varied clinical presentation and prognosis. The most common subtypes of cutaneous T-cell lymphomas are the epidermotropic variants mycosis fungoides and Sezary syndrome. Treatment of mycosis fungoides has encompassed a variety of modalities including the use of retinoids with several studies evaluating their efficacy. The reported benefits and duration of response have varied in published data. The biological effect of retinoids is mediated by specific receptor families, retinoic acid receptor (RAR) and retinoic X receptor (RXR), with subsequently altered gene expression. There are no data available on cutaneous T-cell lymphomas that compare RAR and RXR retinoids. The objective of our retrospective, nonrandomized, single-center study was to compare the response, survival outcomes, and toxic effects in our phase II trial of the RAR-specific retinoid, all-trans retinoic acid, with clinical use of the RXR-specific retinoid, bexarotene, in patients with mycosis fungoides/Sezary syndrome who have relapsed. There was no statistical difference in response rates (12% vs 21%), response duration (20.5 vs 7.3 months), event-free survival time (4 vs 5 months), or median survival when corrected for length of follow-up. Both have favorable toxicity profiles that can be managed with medications. The toxicity profile caused by bexarotene seems to be more limited to laboratory values and better tolerated, although generally associated with more severe grades of toxicity. In conclusion, both retinoids have modest objective response rates and, therefore, most likely will have limited impact as monotherapeutic agents. However, the immunomodulatory effects of RAR and RXR retinoids provide a rational basis for using retinoids in combination with other biologic immune response modifiers, phototherapy, or cytotoxic chemotherapy.

Anticancer Res. 2002 Mar-Apr;22(2A):883-8.

The effect of a water-dispersible beta-carotene formulation on the prevention of age-related lymphoid neoplasms in mice.

Riondel J, Wong HK, Glise D, Ducros V, Favier A.

There is currently a great interest in the efficiency of micronutrients against age-associated disorders. The present study aimed to evaluate the efficacy of beta-carotene on the incidence of lymphoid neoplasia, a fatal pathology associated with OFI mouse ageing. Beta-carotene, given as a water-dispersible preparation to 8-month-old mice, on a four month follow-up study, significantly reduced the incidence of neoplasm (12.5% versus 50% for controls). Evaluation of the parameters of oxidative stress showed a highly-significant reduction of the antioxidant defenses in the liver of cancer mice when compared to healthy controls (78% decrease in GSH-Px activity and 47% decrease of the ratio GSH/GSSG). Liver GSH-Px activity was 35% higher in old than in young mice, which correlated with higher (41%) plasma Se level. In conclusion beta-carotene improved the antioxidant status of the mice, causing a 4.5-fold increase in the liver GSH/GSSG ratio, an effect which was probably responsible for the lowered incidence of neoplasia observed.

Best Pract Res Clin Haematol. 2003 Sep;16(3):433-51.

Choice of chemotherapy in induction, consolidation and maintenance in acute promyelocytic leukaemia.

Sanz MA, Martin G, Lo Coco F.

Cure of acute promyelocytic leukaemia (APL) is now a reality for most patients through the use of combined all-trans retinoic acid (ATRA) and chemotherapy. The simultaneous administration of ATRA and anthracycline-based chemotherapy is currently considered the most appropriate induction therapy. However, no consensus has been reached on the consolidation strategy. Therapeutic efficacy apparently did not differ according to the number of cycles and types of drug combined with anthracyclines. Encouraging results have been reported recently using less-intensive chemotherapy with anthracyclines alone, leading to a significant reduction in treatment-related toxicity during the consolidation phase and a high degree of compliance. Some ongoing risk-adapted protocols are now exploring the potential synergistic effect of ATRA and chemotherapy given simultaneously in consolidation. Preliminary data suggest that higher molecular remission rates post-consolidation and improved outcome may be obtained through this strategy. Persistence or recurrence of molecular disease at the end of consolidation is strongly associated with impending relapse and poor prognosis, indicating the need for further aggressive therapy. As for maintenance therapy, once demonstrated, the advantage of using ATRA with or without low-dose methotrexate and 6-mercaptopurine has encouraged most groups to incorporate such treatment into their protocols for APL.

Annu Rev Nutr. 2004;24:201-21.

Retinoic acid receptors and cancers.

Soprano DR, Qin P, Soprano KJ.

Studies utilizing experimental animals, epidemiological approaches, cellular models, and clinical trials all provide evidence that retinoic acid and some of its synthetic derivatives (retinoids) are useful pharmacological agents in cancer therapy and prevention. In this chapter, we first review the current knowledge of retinoic acid receptors (RARs) and their role in mediating the actions of retinoic acid. We then focus on a discussion of RARalpha and acute promyelocytic leukemia followed by a discussion of the role of RARs, in particular RARbeta expression, in other cancer types. Loss of normal RAR function in the presence of physiological levels of RA (either due to alterations in the protein structure or level of expression) is associated with a variety of different cancers. In some cases treatment with pharmacological doses of RA can be effective.

Br J Haematol. 1993 Dec;85(4):826-8.

Retinoic acid-induced apoptosis and regression of a refractory Epstein-Barr virus-containing T cell lymphoma expressing multidrug-resistance phenotypes.

Su IJ, Cheng AL, Tsai TF, Lay JD.

The virus-associated T cell leukaemias/lymphomas are characterized by a poor prognosis primarily because of the rapid emergence of drug resistance which may lead to failure of subsequent chemotherapy. We report here a case of Epstein-Barr virus-associated T cell lymphoma which relapsed soon after chemotherapy and radiotherapy. The neoplastic cells of the relapsed tumour expressed high levels of multi-drug resistance gene (mdr1)-related P-glycoprotein and glutathione-S-transferase-pi, both of which were absent in the pre-chemotherapy tumour tissues. Empirical treatment with oral 13-cis-retinoic acid (RA) was then given with subsequent complete disappearance of the tumour. The therapeutic effect of RA appears to act through an apoptotic process. In accordance with our previous report of a successful salvage of a refractory Ki-1 large cell lymphoma. RA appears to be a potentially useful drug for some specific type T-cell lymphomas.

Semin Hematol. 2004 Apr;41(2 Suppl 4):27-32.

Acute promyelocytic leukemia as a paradigm for targeted therapy.

Tallman MS.

Substantial progress has occurred in the treatment of acute promyelocytic leukemia (APL) because of improved understanding of the pathophysiology of the disease and identification of a molecular target. Novel agents such as all-trans retinoic acid (ATRA) (alone or combined with chemotherapy) and, more recently, arsenic trioxide have produced complete remission in most patients with newly diagnosed APL and/or relapsed or refractory disease, respectively. Use of these targeted therapies has resulted in evolution of the disease from one that was historically one of the most fatal subtypes of acute myeloid leukemia (AML) to one that appears curable in 70% to 80% of patients. The targeted approach to treatment of this disease can serve as a paradigm for the treatment of other leukemias.

Cancer Biother Radiopharm. 2001 Apr;16(2):171-7.

Cyclophosphamide plus somatostatin, bromocriptin, retinoids, melatonin and ACTH in the treatment of low-grade non-Hodgkin's lymphomas at advanced stage: results of a phase II trial.

Todisco M, Casaccia P, Rossi N.

PURPOSE: Somatostatin, prolactin, retinoids, melatonin and ACTH have been shown to influence the lymphatic growth, and the action of the cyclophosphamide in lymphoproliferative disorders is well known. This provided the rationale to conduct, in patients with low-grade non-Hodgkin's lymphomas (NHL), a phase II trial of a combined association of cyclophosphamide, somatostatin, bromocriptin, retinoids, melatonin and ACTH. PATIENTS AND METHODS: Twenty patients with a diagnosis of low-grade NHL, stage III or IV, were included in this study. Patients received for one month the following treatment: cyclophosphamide, somatostatin, bromocriptin, retinoids, melatonin, and ACTH. The therapy was continued for two additional months in patients with stable or responding disease. After three months, the responding patients continued the therapy for three months and more. RESULTS: Twenty patients were assessable for toxicity and response; 70% (14 of 20 patients; 95% confidence interval [CI], 50% to 90%) had a partial response; 20% (4 of 20) had stable disease, and 10% (2 of 20) progressed on therapy. Going on with the treatment, none of the 14 patients with partial response had a disease progression (average follow-up time of 21 months, range, 7 to 25), and 50% of these patients had a complete response; among 4 patients with stable disease, 25% (1 of 4) had a partial response and 75% (3 of 4) progressed on therapy (mean time to progression [TTP] 14.3 months, range, 7 to 21). The toxicity was very mild, the most common side effects being drowsiness, diarrhea and hyperglycemia. CONCLUSIONS: The association of cyclophosphamide, somatostatin, bromocriptin, retinoids, melatonin, and ACTH is well tolerated and effective in treatment of low-grade NHL at advanced stage.

Cell Growth Differ. 1995 Jun;6(6):655-63.

Growth inhibition and apoptosis of RL human B lymphoma cells by vitamin E succinate and retinoic acid: role for transforming growth factor beta.

Turley JM, Funakoshi S, Ruscetti FW, Kasper J, Murphy WJ, Longo DL, Birchenall-Roberts MC.

Vitamin E succinate (VES) and all-trans-retinoic acid (RA) were determined to be growth inhibitory for B lymphoma cells in vitro. RL, an Epstein-Barr virus-negative human cell line, was growth suppressed 87% with VES (5 micrograms/ml) and 58% with RA (10(-6) M); both agents blocked the cells in G1 of the cell cycle. The antiproliferative effect of VES seems to be independent of its potential antioxidant property because both fat- and water-soluble antioxidants were found to have no effect on RL cell proliferation. VES and RA increased IgM antibody concentrations in cell supernatants 5.8- and 9.9-fold, respectively. DNA fragmentation and flow cytometry studies showed VES- and RA-induced apoptosis in RL cells. VES- and RA-treated RL cells gradually underwent apoptosis over time with maximal induction occurring at days 6 and 5 of culture, respectively. A role for transforming growth factor beta in VES- and RA-mediated RL growth suppression is indicated by increased ligand and type II receptor protein expression. Furthermore, neutralizing antibodies to transforming growth factor beta 1 partially blocked the growth suppressive action of both VES and RA, thus suggesting that a TGF-beta autocrine negative loop was involved in VES and RA suppression of RL cell growth.

Cell Adhes Commun. 2000 May;7(5):423-40.

Differentiation, proliferation and adhesion of human neuroblastoma cells after treatment with retinoic acid.

Voigt A, Hartmann P, Zintl F.

Because of the known property of spontaneous regression in stage IVS of neuroblastoma all attempts are made to elucidate whether differentiation inducers possibly could be applied for neuroblastoma therapy. Here we examined the influence of retinoic acid (RA) in vitro on differentiation, proliferation and adhesion of 10 permanent and 4 primary cell lines as well as of several SCID-mouse tumour transplants. In general, after RA treatment morphologically different cell types which are characteristic for neuroblastoma cells have changed. N (neuronal)-type cells prolonged their neuronal processes, whereas S (epithelial, substrate-adherent, Schwann cell-like)-type cells lost their adherence to substratum and became apoptotic. Additionally, the reactions of all neuroblastoma cell lines with monoclonal antibodies against beta-tubulin (for neuronal cells) and glial fibrillary acidic protein (for epithelial cells) were determined. The anti-proliferative effect of all-trans-RA as well as 13-cis-RA was more profound in S-type cells (up to 40% in primary cell lines). To elucidate the role of adhesion molecules during neuronal cell differentiation, we have analysed the adhesion of neuroblastoma cells on poly-D-lysin-precoated plates under RA influence. While N-type cells displayed an increased adhesion, all S-type cell lines as well as all primary cell lines exhibited a reduced adhesion (IMR-5 and IMR-32: $p < 0.001$; JW, SR and PM: $p < 0.05$). RA treatment increased predominantly the tested antigens (HCAM, ICAM-1, NCAM, PECAM-1, VCAM-1, cadherin, FGF-R, IGF-R, NGF-R, TGF-beta/1, NF200, NF160, NF68, NSE, HLA-ABC) in all cell lines independently of their phenotypes (TGF-beta/1: $p < 0.001$; NF68: $p < 0.01$; PECAM-1 and NGF-R: $p < 0.05$). In recultured SCID-mouse-passaged tumour cells antigens were down-regulated (FGF-R: $p < 0.01$), but increased again after RA influence (TGF-beta/1: $p < 0.05$). In summary, the RA differentiation model demonstrates the possibility to interfere in cell adhesion and to diminish growth potential both in N-type as well as S-type neuroblastoma cells.

Exp Hematol. 2000 Dec;28(12):1441-50.

Retinoic acid-induced apoptotic pathway in T-cell lymphoma: Identification of four groups of genes with differential biological functions.

Wang KC, Cheng AL, Chuang SE, Hsu HC, Su IJ.

Retinoic acid (RA) has been used to induce the regression of refractory T-cell lymphoma. In vitro and in vivo studies have shown that RA exerts this effect through the induction of apoptosis. This study was designed to investigate the molecular pathway of RA-induced apoptosis in T-lymphoma cell lines.RA-induced apoptosis was verified by morphology, flow cytometry, and DNA ladder analysis. Differential display method using a combination of 12 poly(A)-anchored primers and 20 arbitrary primers was adopted for gene cloning. Total RNAs were extracted from H9 cell line at 0, 6, 12, and 24 hours after All-trans RA (ATRA) treatment and the serial expression patterns of the candidate fragments were recognized. The cloned gene fragments were then analyzed and confirmed by Northern blot analysis on H9 and SR786 cell lines.ATRA-induced apoptosis of T-cell lymphoma was protein synthesis-dependent. The execution or irreversible phase of apoptosis appeared to occur at 6-12 hours of RA treatment. Among the 60,000 arbitrarily displayed bands, 25 of 250 candidate fragments were selected for further cloning and sequencing. A total of 14 clones could be matched to known genes and were categorized into four groups: A) transcription factors: prothymosin, CA150, p78 serine/threonine kinase, IL-1beta-stimulating gene, glucocorticoid receptor, MLN64/CAB1, gastrin-binding protein, and polypeptide from glioblastoma; B) chaperone: 90 kDa heat shock protein; C) ion channel: chloride channel protein 3; and D) cytoskeleton: cytovillin2/ezrin and vimentin. Another two clones of genes were of unrecognized functions. The remaining 11 clones belonged to unmatched or novel genes. The expression of these genes varied, either upregulated or downregulated, in response to ATRA treatment.RA-induced apoptosis may involve a cascade of genes that are related to transcription regulation, stress response, housekeeping, and the execution of apoptosis. The clarification of the RA-induced apoptotic pathway will help us to understand the molecular mechanism of cancer differentiation agents.

Chin Med J (Engl). 2001 Sep;114(9):958-61.

Growth inhibition of gastric cancer cells by all-trans retinoic acid through arresting cell cycle progression.

Wu Q, Chen Z, Su W.

OBJECTIVE: To investigate the mechanism of all-trans retinoic acid (ATRA) on the regulation of the cell cycle in gastric cancer cells. METHODS: The protein level was detected by Western blot. Immunoprecipitation was used in protein kinase activity determination. Cell growth and cell cycle phase were examined by MTT assay and flow-cytometric analysis, respectively. RESULTS: ATRA could effectively induce G0/G1 arrest and inhibit cell growth in certain human gastric cancer cell lines. ATRA might induce p21WAF1/CIP1 expression in ATRA-sensitive cell lines through p53-dependent and p53-independent pathways. Induction of p21WAF1/CIP1 caused decrease in CDK4 and CDK2 activities independent of CDK4 and CDK2 protein expression levels. In addition, the dephosphorylated form of Rb protein increased because of the down-regulation of CDK4 and CDK2 activities by ATRA. CONCLUSIONS: Growth inhibition on gastric cancer cells by ATRA occurs through the regulation of relevant proteins leading to the arrest of cell cycle progression.

Leuk Lymphoma. 2000 Dec;40(1-2):79-85.

Experience with 9-cis retinoic acid in patients with relapsed and refractory non-Hodgkin's lymphoma.

Younes A, Cristofanilli M, McLaughlin P, Hagemeister FB, Weber D, Mesina O, Cabanillas F.

We conducted a phase II study to determine the efficacy and toxicity of 9-cis-retinoic acid (9-cis RA), a pan-retinoid receptor agonist, in the treatment of patients with relapsed and refractory NHL. Patients were eligible if they had histologically documented relapsed or refractory T cell or indolent B cell NHL. The first three patients enrolled received 70 mg/m2 of 9-cis RA orally twice a day, but the remaining patients received a single oral daily dose of 100 mg/m2. After 6 weeks of therapy, tumor response was assessed objectively. Response rate and toxicity were determined in all 29 eligible patients based on an intent-to-treat analysis. Four patients (14%) responded (3 PRs and 1 CR; 95% CI 4%-33%). One patient had a minor response, and eight had stable disease. Responses were observed in two (11%) of 19 patients with B-cell lymphoma and in two (20%) of 10 patients with T-cell lymphoma. The median time-to-treatment failure for the 29 eligible patients was 8 weeks. The most frequent toxic effects were dry skin, headache, hypertriglyceridemia, and hypercalcemia. Five patients discontinued therapy due to toxic side effects, but no toxic deaths occurred during the study. We conclude that 9-cis RA has a modest activity in relapsed and refractory NHL. In this study, responses were observed in patients with B-cell lymphomas and those with T-cell lymphomas.

Dermatol Ther. 2003;16(4):322-30.

Retinoids: therapeutic applications and mechanisms of action in cutaneous T-cell lymphoma.

Zhang C, Duvic M.

Retinoids, natural and synthetic derivatives of vitamin A, are biological regulators of differentiation, proliferation, apoptosis, and immune response. Retinoic-acid-receptor-selective retinoids (all-trans retinoic acid, 13-cis-retinoic acid, and the synthetic analogs isotretinoin, etretinate and acitretin) have been used for years as monotherapy and/or in combination for treatment of cutaneous T-cell lymphoma (CTCL). Orally administered bexarotene, the first synthetic highly selective retinoid-X-receptor retinoid to be approved by the FDA for CTCL, was shown to be active against the cutaneous manifestations of all stages of CTCL. The topical gel formulation was also effective for early cutaneous manifestations of CTCL or as an adjunct to systemic or phototherapy. Bexarotene treatment induces apoptosis of CTCL cells with down-regulation of its receptors and of survivin, an inhibitor of apoptosis. Identification of new receptor subtype-selective retinoids, combination of various receptor-selective retinoids or other agents, and a new drug delivery system may improve the clinical efficacy of retinoids in the future.

Tumour Biol. 2001 Jul-Aug;22(4):247-53.

Retinoic acids reduce matrilysin (matrix metalloproteinase 7) and inhibit tumor cell invasion in human colon cancer.

Adachi Y, Itoh F, Yamamoto H, Iku S, Matsuno K, Arimura Y, Imai K.

All-trans retinoic acid (ATRA), 9-cis retinoic acid and 13-cis retinoic acid are naturally occurring retinoids used in the prevention and therapy of various preneoplastic and neoplastic diseases. It was previously reported that matrilysin, one of the matrix metalloproteinases (MMP-7), plays a critical role in the invasion and metastasis of gastrointestinal cancers. Moreover, it has been shown that ATRA downregulates matrilysin expression and prevents in vitro invasion by colon cancer cells. In this study, three retinoids were used, both in Matrigel invasion assays and in subcutaneous xenografts in mice, to evaluate the effects of retinoids on invasion by colon cancer cell lines (CHC-Y1, DLD-1, HT-29, BM314, CaR-1 and WiDr). All three retinoic acids tested reduced matrilysin expression and suppressed the invasiveness of colon cancer cell lines in vitro. Retinoic acids also reduced tumor invasion in mice without influencing tumor growth. Matrilysin expression in these tumors was clearly reduced. These data support the use of retinoic acids as useful reagents to manage patients with colorectal carcinoma.

Neurochem Res. 2001 Jan;26(1):83-8.

Effect of retinoic acid on the Ca2+-independent phospholipase A2 in nuclei of LA-N-1 neuroblastoma cells.

Antony P, Freysz L, Horrocks LA, Farooqui AA.

LA-N-1 neuroblastoma cell cultures contain Ca2+-independent phospholipases A2 hydrolyzing phosphatidylethanolamine and ethanolamine plasmalogens. These enzymes differ from each other in their molecular mass, substrate specificity, and kinetic properties. Subcellular distribution studies have indicated that the activity of these phospholipases is not only localized in the cytosol but also in non-nuclear membranes and in nuclei. The treatment of LA-N-1 neuroblastoma cell cultures with retinoic acid results in a marked stimulation of Ca2+-independent phospholipases A2 hydrolyzing phospha-tidylethanolamine and plasmenylethanolamine. The increase of the activities of both enzymes was first observed in nuclei followed by those present in the cytosol. No effect of retinoic acid on either phospholipase activity could be observed in non-nuclear membranes. The stimulation of these enzymes may be involved in the generation and regulation of arachidonic acid and its metabolites during differentiation.

Anticancer Res. 2003 Jan-Feb;23(1A):471-3.

All-trans-retinoic acid activates caspase-1 in a dose-dependent manner in cervical squamous carcinoma cells.

Arany I, Ember IA, Tyring SK.

Earlier we observed that all-trans-retinoic acid (ATRA) dose-dependently suppressed the growth of cervical carcinoma cells. Suppression of growth required sustained activation of interferon regulatory factor 1 (IRF-1), which was achieved by high-dose (10(-4) M), but not low-dose (10(-6) M), ATRA treatment. In this paper we examine the role of IRF-1 in cell death that accompanied the growth suppression in high-dose ATRA-treated cells. We found that high-dose, but not low-dose, ATRA treatment activated caspase-1 in those cervical carcinoma cells. Transient transfection of an antisense-IRF-1 construct diminished high-dose ATRA-mediated caspase-1 activation. On the other hand, ATRA was not able to induce caspase-1 expression in a STAT1 (signal transducer and activator of transcription 1) knockout cell line, but transient transfection of STAT1 restored it. These results suggested the importance of both IRF-1 and STAT1 in high-dose ATRA-induced activation of caspase-1. Our results might be useful in the treatment of retinoid-resistant cervical neoplasias.

Anticancer Res. 2003 Jan-Feb;23(1A):495-7.

Dose-dependent activation of p21WAF1 transcription by all-trans-acid in cervical squamous carcinoma cells.

Arany I, Whitehead WE, Ember IA, Tyring SK.

SiHa cervical squamous carcinoma cells were resistant to ATRA-induced growth inhibitory effect at a physiological dose (10(-6) M), but responsive at a pharmacological dose (10(-4) M). The observed growth arrest was associated with increased levels of the interferon regulatory factor-1 (IRF-1). IRF-1 is a known inhibitor of cell growth, and thus our aim was to identify the downstream target of this growth inhibitory function. We found that, as with the induction of IRF-1, levels of p21WAF1 were similarly dose-dependently induced by ATRA. Semiquantitative RT-PCR, Western blotting, gel-shift analysis (EMSA), antisense gene expression and application of a STAT1-knockout cell line demonstrated that activation of the p21WAF1 gene was IRF-1 and STAT1-dependent. We concluded that activation of STAT1 and IRF-1 is crucial for the growth inhibitory action of ATRA, which is associated with the activation of p21WAF1. These results might be useful in chemoprevention of cervical cancers.

Best Pract Res Clin Haematol. 2003 Sep;16(3):419-32.

All-trans retinoic acid in acute promyelocytic leukaemia.

Avvisati G, Tallman MS.

The vitamin A derivative, all-trans retinoic acid (ATRA), induces differentiation of leukaemic promyelocytes in patients with acute promyelocytic leukaemia (APL). As a result, the majority of patients achieve complete remission either with ATRA alone or with combined ATRA and chemotherapy. The most important complication is the retinoic acid syndrome, which is usually successfully treated with the early administration of dexamethasone. Prospective randomized trials have shown that ATRA is better than conventional chemotherapy in newly diagnosed patients, that ATRA combined with chemotherapy confers an advantage with respect to relapse rate, compared to ATRA alone for induction followed by chemotherapy for consolidation, and that maintenance therapy with ATRA or ATRA plus low-dose chemotherapy is beneficial. The presence of adverse prognostic factors, including older age, presenting white blood cell count and platelet count, expression of CD56 and presence of mutations in the FLT3 gene, identify patients at risk for relapse for whom new strategies are needed.

Br J Dermatol. 2003 Mar;148(3):424-33.

Early vitronectin receptor downregulation in a melanoma cell line during all-trans retinoic acid-induced apoptosis.

Baroni A, Paoletti I, Silvestri I, Buommino E, Carriero MV.

BACKGROUND: Recent evidence assigns the vitronectin receptors (VnRs) an important role in regulating tumour cell invasion and dissemination. In vivo and in vitro studies document that all trans-retinoid acids (ATRAs) inhibit growth-inducing apoptosis in melanomas. OBJECTIVES: We have analysed the effects of ATRA treatment on melanoma cell adhesion and motility. METHODS: Human M14 melanoma cells were treated with 10 micromol L-1 ATRA for different times and stained with rhodamine-phalloidin to analyse the effect of treatment on cytoskeleton organization. Cell adhesion and cell migration assays were performed to analyse the role of VnRs in the ATRA-induced early stages of apoptosis. VnR expression was evaluated by Western blot, immunoprecipitation and immunocytochemistry assays. RESULTS: First, using an annexin V assay, we found that apoptosis was triggered by 48 h with 10 micromol L-1 ATRA exposure. At this time point, decrease in the F-actin polymerization as well as inhibition of cell adhesive ability to vitronectin (Vn) was exerted by ATRA treatment. In the presence of serum, exposure to 10 micromol L-1 ATRA for 48 h produced a dramatic inhibition of the cell adhesion ability that was comparable with that exerted by untreated cells preincubated with anti-alpha(v)beta(3) or anti-alpha(v)beta(5) VnR monoclonal antibodies. Functionally, the treatment of melanoma cells with 10 micromol L-1 ATRA for 48 h causes an inhibition of directional cell migration towards Vn-coated filters. Therefore, we analysed the effect of ATRA on the VnR expression. Both alpha(v)beta(3) and alpha(v)beta(5) VnR levels were reduced upon exposure to 10 micromol L-1 ATRA for 48 h as shown by Western blot, immunoprecipitation and immunocytochemistry assays. CONCLUSIONS: Altogether, our data indicate that treatment of M14 melanoma cells with ATRA downregulates VnR expression and that this reduction is closely correlated with the ATRA-dependent inhibition of actin-fibre organization, cell adhesion and migration. Although the mechanism by which ATRA regulates the expression of VnR in M14 melanoma cells needs further elucidation, this system may represent a model for understanding the molecular basis of ATRA therapy in melanoma.

Phytomedicine. 2000 Apr;7(2):151-9.

Beta-carotene prolongs survival, decreases lipid peroxidation and enhances glutathione status in transplantable murine lymphoma.

Basu M, Banerjee A, Bhattacharya UK, Bishayee A, Chatterjee M.

Carotenoids of dietary origin have recently been the subject of renewed research interest because of epidemiological evidence indicating an inverse relationship between intake of carotenoids-rich plant substances and risk of certain cancers. This study was attempted to understand the biological actions of dietary beta-carotene (BC) on Dalton's lymphoma (DL), a rapidly proliferating transplantable tumor, in effecting the survival of the lymphoma-bearing mice. The glutathione (GSH) level and the extent of lipid peroxidation in the liver, kidney and brain were monitored in BC-treated (100 mg/kg food) mice transplanted with DL. These markers showed substantial alterations during the whole length of tumor progression in lymphoma-bearing mice without BC supplementation. When treated with BC, both malondialdehyde contents (evidence of lipid peroxidation) and the GSH levels in different organs were found to be closer to normal values in the initial period of tumor progression. BC-mediated protection against lipid peroxidation was maximally found to be in hepatic tissue throughout the study following DL transplantation. This was fairly reflected in the higher BC concentration in hepatic tissue of BC-treated lymphoma group compared to untreated lymphoma control. Significantly higher survival time (51-55 days) was observed in BC-treated animals in comparison to their untreated DL counterparts (35-38 days). The prolonged survival observed in the BC-supplemented animals may be attributed to the higher resistance offered by animals receiving BC towards lipid peroxidation-related tissue injury.

Biochim Biophys Acta. 2005 May 30;1740(2):170-8. Epub 2005 Jan 25.

Cancer prevention by retinoids and carotenoids: independent action on a common target.

Bertram JS, Vine AL.

Virtually all human tumors are deficient in gap junctional communication (GJC) and the restoration of GJC by forced expression of connexins reduces indices of neoplasia. The expression of connexin 43 (Cx43) is upregulated by cancer-preventive retinoids and carotenoids which correlates with the suppression of carcinogen-induced transformation in 10T1/2 cells. However, the molecular mechanism for upregulated expression is poorly understood. The retinoic acid receptor antagonist, Ro 41-5253, suppressed retinoid-induced Cx43 protein expression in 10T1/2 cells and the induction of a Cx43 luciferase reporter construct in F9 cells, but did not suppress protein expression or reporter activity induced by the non-pro-vitamin A carotenoid astaxanthin. In contrast, Cx43 induction by astaxanthin, but not by a RAR-specific retinoid, was inhibited by GW9662, a PPAR-gamma antagonist. Neither compound required protein synthesis for the induction of Cx43 mRNA, nor was the 5.0 h half-life of Cx43 mRNA altered, indicating direct transcriptional activation. The responsive region was found within -158 bp and +209 bp of the transcription start site. Site directed mutagenesis of a GC-box in this region increased basal levels of transcription and loss of retinoid responsiveness. Simultaneous treatment with a retinoid and beta-carotene or astaxanthin resulted in supra-additive Cx43 expression, again indicating separate mechanisms of gene regulation.

Leuk Lymphoma. 1997 Mar;25(1-2):169-78.

Growth modulation of freshly isolated non-Hodgkin's B-lymphoma cells induced by various cytokines and all-trans-retinoic-acid.

Bonnefoix T, Gressin R, Jacrot M, Perron P, Swiercz P, Chaffanjon P, Sotto JJ.

We investigated the potential of ten cytokines (IL2, IL3, IL4, IL6, IL10, IL13, G-CSF, GM-CSF, interferon alpha, interferon gamma) and all-trans-retinoic acid to modulate the spontaneous proliferative response in vitro of purified B-non Hodgkin's lymphoma cells of various histological subtypes. 19 malignant lymph nodes were studied. In each case the growth could be influenced by several of these modulators. Cytokines most often implicated were interferon gamma (14/19 cases, 73.7%), IL4 (13/19 cases, 68.4%), interferon alpha (12/19 cases, 63.1%). IL2 (9/19 cases, 47.3%), IL6, IL10, IL13 and ATRA were less frequently involved (6/19 cases, 31.6%) and hematopoietic growth factors (IL3, GM-CSF, G-CSF) were rarely implicated (2/19 cases, 10.5%). The values of growth stimulation ranged from a 1.1-fold to a 6.1-fold increase, and the values of growth inhibition ranged from 15% to 98%. Each cytokine could be either inhibitory or stimulatory depending on the sample analyzed, and no relationship could be found with the histological subtype. Two notable exceptions were IL2, displaying exclusively a positive effect, and ATRA displaying exclusively a negative effect. Overall, these results may have strong implications for future clinical studies using cytokines in the treatment of lymphomas. Ideally, the pattern of in vitro growth response to cytokines or ATRA should be determined individually before undertaking any cytokine treatment.

Clin Lymphoma. 2000 Nov;1 Suppl 1:S41-4.

Historical perspective on the use of retinoids in cutaneous T-cell lymphoma (CTCL).

Burg G, Dummer R.

Vitamin A and its analogues influence differentiation and proliferation and may also alter immune responses. Limited clinical efficacy of these compounds given alone or as part of a combination therapy has been shown in various types of cutaneous T-cell lymphoma (CTCL), including mycosis fungoides, Sezary syndrome, and prelymphomatous disorders such as parapsoriasis en plaques. Compounds used mostly in small, nonrandomized trials are isotretinoin (13-cis-retinoic acid), etretinate, acitretin, and all-trans-retinoic acid. Clinical responses have been found despite persistent residual disease with atypical lymphocytes in various compartments. The exact mechanism of action of retinoids in CTCL is unclear and depends on the presence of retinoid receptors on the tumor cells, which is variable in different forms of CTCL. Therapies combining retinoids with psoralen-ultraviolet A or with interferons may have a synergistic effect, which deserves confirmation through randomized trials in the future.

Cancer Chemother Pharmacol. 2001;47(2):126-32.

Upregulation of gap junctional intercellular communication and connexin 43 expression by cyclic-AMP and all-trans-retinoic acid is associated with glutathione depletion and chemosensitivity in neuroblastoma cells.

Carystinos GD, Alaoui-Jamali MA, Phipps J, Yen L, Batist G.

PURPOSE: Downregulation of gap junctional intercellular communication (GJIC) has been implicated in carcinogenesis. This is a result of altered expression of connexins, the proteins that mediate GJIC, including connexin 43 (Cx43). Our aim was to evaluate the effect of known inducers of Cx43 on the chemosensitivity of the human neuroblastoma cell line IMR-32 to chemotherapeutic agents. METHODS: We examined the effect of dibutyryl-cyclic AMP (db-cAMP) and all-trans-retinoic acid (tRA) on Cx43 and GJIC, glutathione (GSH) and gamma-glutamyl-cysteine-synthetase (gamma-GCS) levels, and glutathione S-transferase (GST) activity. Finally, we performed cell survival assays to measure the response of IMR-32 cells to the chemotherapeutic drugs doxorubicin, melphalan and bis-chloronitrosourea (BCNU), after treatment with db-cAMP and/or tRA. RESULTS: Exposure to db-cAMP led to the upregulation of GJIC and Cx43 expression and phosphorylation. On the other hand, exposure to tRA led to the upregulation of GJIC but Cx43 expression and phosphorylation were not greatly affected. The combination of both agents was more potent in inducing GJIC in comparison to treatment with db-cAMP or tRA alone. Treatment with db-cAMP, but not with tRA, was associated with a significant increase in the cytotoxic effects of the anticancer drugs doxorubicin, melphalan and BCNU as shown by a decrease in their IC50 values. Concomitant exposure to db-cAMP and tRA, however, had a more pronounced effect on cell sensitization to chemotherapy drugs (particularly doxorubicin) than exposure to db-cAMP or tRA alone. Under the db-cAMP and tRA treatment conditions (which upregulate GJIC and modulate drug response), GSH levels were significantly reduced while the levels of GST and gamma-GCS activities remained unchanged. CONCLUSIONS: This study suggests that GJIC plays a role in cellular drug resistance, and highlights the potential use of GJIC modulators in combination with chemotherapy. Also, this is the first study exploring the ability of both db-cAMP and tRA to enhance cell chemosensitivity.

J Formos Med Assoc. 1998 Jun;97(6):420-4.

Response of Epstein-Barr virus-associated Ki-1+ anaplastic large cell lymphoma to 13-cis retinoic acid and interferon alpha.

Chen GS, Chang YF, Chang MC, Tsan KW.

The response of peripheral T-cell lymphoma to 13-cis retinoic acid (13-cis-RA) has been well established, especially in Ki-1+ anaplastic large cell lymphoma (ALCL) confined to the skin. Here, we report the use of 13-cis-RA in combination with interferon alpha in a patient with refractory ALCL. The patient, an 18-year-old man, suffered from retroperitoneal, hepatic, and splenic ALCL. Reactive hemophagocytic syndrome also developed. Active Epstein-Barr virus infection was demonstrated by serologic tests and in situ hybridization of Epstein-Barr virus early RNA-1. Although high-dose intravenous immunoglobulin (IgG), etoposide, and steroids were administered, only chemotherapy (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) successfully controlled the progress of hemophagocytosis. However, the retroperitoneal mass and splenic tumor did not show a satisfactory response to three cycles of chemotherapy. Hence, interferon 4.5 MU/m2 every other day with 13-cis-RA 1 mg/kg/day was instituted. Abdominal computed tomogram after 58 days of treatment revealed that the tumor had significantly reduced in size. Bone marrow biopsy demonstrated alleviation of hemophagocytosis as well. However, lymphoma cells had begun to infiltrate the bone marrow. Our findings suggest that 13-cis-RA and interferon alpha may be partially effective in treating ALCL.

J Clin Oncol. 1994 Jun;12(6):1185-92.

Use of retinoic acids in the treatment of peripheral T-cell lymphoma: a pilot study.

Cheng AL, Su IJ, Chen CC, Tien HF, Lay JD, Chen BR, Pu YS, Hong RL, Shen MC, Wang CH, et al.

PURPOSE: We have systemically analyzed, both in vitro and in vivo, the effect of 13-cis-retinoic acids (RA) on non-Hodgkin's lymphoma (NHL). METHODS: The in vitro growth-inhibitory effect of 13-cis-RA was examined in 11 (T cell, five; B cell, six) lymphoma cell lines by a tetrazolium colorimetric assay. A pilot clinical trial with oral 13-cis-RA 1 mg/kg/d was conducted in a selected group of 18 lymphoma patients, of whom 16 had failed to respond to at least one regimen of intensive chemotherapy. The in vitro and in vivo effects of 13-cis-RA were correlated with immunophenotypes, RA-induced changes of morphology, and patterns of DNA fragmentation of the lymphoma cells. RESULTS: Four of five T-lymphoma cell lines and none of six B-lymphoma cell lines were sensitive (concentration of 50% growth inhibition [IC50] < 1.5 microns) to 13-cis-RA (P = .015). In the clinical trial, five (two Ki-1, one angioinvasive type, one diffuse mixed cell, and one diffuse large cell) complete remissions and one (Ki1) partial remission were observed in 12 patients with peripheral T-cell lymphoma (PTCL), while none of six patients with B-cell lymphoma responded to 13-cis-RA. 13-cis-RA-induced cellular differentiation and apoptosis, as evidenced by the more mature morphology, characteristic nuclear condensation, and DNA ladder pattern signifying internucleosomal fragmentation, were demonstrated in the sensitive cell lines, as well as in the remitting lymphoma tissues. CONCLUSION: The 13-cis-RA appears to be active on lymphomas of T-lineage and their therapeutic indication may be extended to include some subtypes of PTCL. The mechanisms of action are related to differentiation and apoptosis of lymphoma cells. There appears to be no cross-resistance between 13-cis-RA and conventional chemotherapy.

Biochem J. 2000 Jun 1;348 Pt 2:473-9.

Bcl-2 accelerates retinoic acid-induced growth arrest and recovery in human gastric cancer cells.

Chou HK, Chen SL, Hsu CT, Chao YC, Tsao YP.

The role of Bcl-2 as an anti-apoptotic protein has been well documented. In the present work, we present evidence that Bcl-2 may also be involved in cell growth regulation. SC-M1 is an unique cell line which responds to retinoic acid (RA) treatment with reversible growth arrest [Shyu, Jiang, Huang, Chang, Wu, Roffler and Yeh (1995) Eur. J. Cancer 31, 237-243]. In this study, when treated with RA, SC-M1/Bcl2 cells, which were generated by transfecting SC-M1 cells with bcl-2 DNA, were growth-arrested two days earlier than SC-M1/neo cells, which were generated by transfecting SC-M1 cells with vector DNA. This indicates that Bcl-2 accelerates RA-induced growth arrest. In addition to the accelerated growth arrest, RA-treated SC-M1/Bcl2 cells also recovered from growth arrest two days faster than SC-M1/neo cells after the removal of RA. Previously, we had identified the cyclin-dependent kinase inhibitor p21((WAF1/CIP1)) (p21) as a mediator of RA-induced growth arrest [Tsao, Li, Kuo, Liu and Chen (1996) Biochem. J. 317, 707-711]. In a search for the mechanism by which Bcl-2 affects growth regulation, we found that p21 gene expression was more prominent in SC-M1/Bcl2 cells than in SC-M1/neo cells in the presence of RA, but when RA was removed, p21 gene expression levels in SC-M1/Bcl2 cells were also reduced earlier than in SC-M1/neo cells. The present report is the first to show that Bcl-2 accelerates not only growth arrest but also recovery from growth arrest. Moreover, the close correlation between the effect of Bcl-2 on both RA-induced growth arrest and RA-induced p21 gene expression suggests the possibility that Bcl-2 affects cell growth through the mechanism of p21.

Cancer. 1996 Oct 15;78(8):1805-12.

Clinicopathologic, cytogenetic, and molecular studies of 13 Chinese Patients with Ki-1 anaplastic large cell lymphoma. Special emphasis on the tumor response to 13-cis retinoic acid.

Chou WC, Su IJ, Tien HF, Liang DC, Wang CH, Chang YC, Cheng AL.

BACKGROUND: The clinicopathologic and molecular features of the newly characterized Ki-1 lymphoma, although well studied in Western countries, are less well described in Asia. METHODS: Pathology material of lymphoma cases, consecutively diagnosed at our institution between 1986 and 1994, was reviewed. The cases fulfilling the diagnostic criteria of Ki-1 lymphoma were selected, and their clinicopathologic features were studied. Immunohistochemistry and cytogenetic studies of the lymphoma tissues, and molecular analysis for nucleophosmin (NPM) gene translocation were performed. RESULTS: A total of 13 cases (2.3%) of Ki-1 large cell lymphoma were identified from a total of 572 cases of non-Hodgkin's lymphoma diagnosed during this period of time. There were 10 men and 3 women with a median age of 43 years (range, 18 to 61 years). The initial presenting sites included the skin alone in five cases, lymph node alone in one case, both skin and lymph node in five cases, and the stomach in one case. All cases had large cell morphology, with the majority of the neoplastic cells expressing Ki-1 antigen (CD30). Except for the case with gastric involvement, all other cases were T-cell lymphomas. One of seven cases examined had chromosomal abnormality of t (2;5). Rearrangement of the NPM gene at chromosome 5 was detected by Southern blot analysis in three of nine cases. Two of seven cases tested by reverse-transcriptase polymerase chain reaction showed fusion of the NPM gene and anaplastic lymphoma kinase gene. Seven (78%) of 9 patients who had received systemic chemotherapy with a standard cyclophosphamide, doxorubicin, vincristine, and prednisolone regimen obtained a complete remission (CR). The median duration of remission was 33 months. Three (60%) of 5 patients, of whom 4 recurred from previous intensive chemotherapy, achieved a prolonged CR with treatment with 13-cis retinoic acid (RA). The median survival of the whole group has not yet been reached at a median follow-up of 40 months. CONCLUSIONS: The clinicopathologic and molecular features of Ki-1 lymphoma of Chinese patients are comparable to those reported from Western countries. 13-cis RA appears to be an effective treatment of Ki-1 lymphoma.

Cancer. 1991 May 15;67(10):2490-4.

13-cis-retinoic acid induces cellular differentiation and durable remission in refractory cutaneous Ki-1 lymphoma.

Chow JM, Cheng AL, Su IJ, Wang CH.

A 35-year-old man with refractory cutaneous Ki-1 lymphoma was salvaged successfully with oral 13-cis-retinoic acid (1 mg/kg/day). He had a complete remission lasting for 20 months before a single nodule recurred on his skin. Excisional biopsy of the recurrent tumor revealed a distinct morphologic change, suggesting cellular differentiation toward a more benign phenotype. No significant side effects were noted except mild xerostomia, bone pain, and hyperlipidemia. The authors believe that 13-cis-retinoic acid should be considered in the treatment of cutaneous Ki-1 lymphoma.

Cancer Res. 1989 Jan 1;49(1):44-50.

Inhibition of Moloney murine lymphoma and sarcoma growth in vivo by dietary retinoids.

Dillehay DL, Shealy YF, Lamon EW.

The effects of dietary retinoids on the growth of Moloney lymphoma (LSTRA) and sarcoma (MSC) in BALB/c mice were evaluated. Transplantable syngeneic Moloney lymphoma and sarcoma tumors are immunogenic. Preimmunization with LSTRA cells provides protection against subsequent challenge and sarcomas spontaneously regress following injection of an appropriate inoculum of MSC cells. In normal mice fed varying concentrations of all-trans-retinoic acid (RA) and given injections of 10(3) LSTRA cells, RA caused a dose-dependent increase in the number of survivors; 50% of the mice fed RA at 50 mg/kg of diet were long-term survivors. All animals died that were fed a control diet and challenged with 10(3) LSTRA cells. Athymic (nu/nu) mice fed RA were not protected against lymphoma growth, whereas euthymic (nu/+) mice were; therefore, the antitumor effect of RA was thymus dependent. Primary immunization with irradiated LSTRA in the presence of RA caused a significant increase in cell-mediated cytotoxicity by spleen cells at 4 days after immunization. However, challenge of animals preimmunized with LSTRA in the presence of dietary RA revealed a dose-dependent inhibition of memory. A significant reduction in MSC growth was also observed in normal mice fed 13-cis-retinoic acid (cRA). A comparison of the primary antilymphoma effect of dietary RA, cRA, N-(all-trans-retinoyl)-DL-leucine (RL), and N-(4-hydroxyphenyl)retinamide (4-HPR) revealed an efficacy hierarchy of RL greater than RA greater than cRA greater than 4-HPR with RL producing 70% long-term survivors at 115 days after challenge with 10(3) LSTRA cells. These studies indicate that retinoids can inhibit the growth of transplantable, retroviral-induced, immunogenic tumors by thymus-dependent mechanisms and that a newly synthesized retinoylamino acid (RL) is more potent than RA at inhibiting Moloney lymphoma growth.

Exp Hematol. 1984 Nov;12(10):768-73.

Effect of retinoic acid on the clonal growth of childhood myeloid and lymphoid leukemias: a pediatric oncology group study.

Findley HW Jr, Steuber CP, Ruymann FB, Culbert S, Ragab AH.

We have studied the effects of retinoic acid (RA) on bone marrow leukemic cells from children with acute nonlymphocytic leukemia (ANLL) at the time of diagnosis, and on cells from four ALL/lymphoma cell lines (common-ALL, pre-B-ALL, T-ALL, and Burkitt's lymphoma) derived from children with these diseases. Cells were cultured in methylcellulose medium with clinically attainable concentrations (0.25-2.0 microM) of RA for two weeks prior to colony and cluster quantitation. Myeloid progenitor cells (CFU-GM) obtained from children with hematologically normal bone marrows were also cultured with RA. Of 19 patients with ANLL whose cells formed colonies, 16 (84%) were inhibited by RA; three patients showed either increased or unchanged colony numbers with RA. RA had a similar effect on both ANLL cluster and colony growth. RA (1-2 microM) also inhibited colony growth of the pre-B-ALL, common-ALL, and Burkitt's lymphoma lines; the T-ALL line and normal bone marrow CFU-GM were not inhibited. The inhibitory effects of RA on pediatric ANLL bone marrow cells and on some ALL/lymphoma cell lines compared with CFU-GM indicate that RA may be of value in the treatment of these malignancies in children.