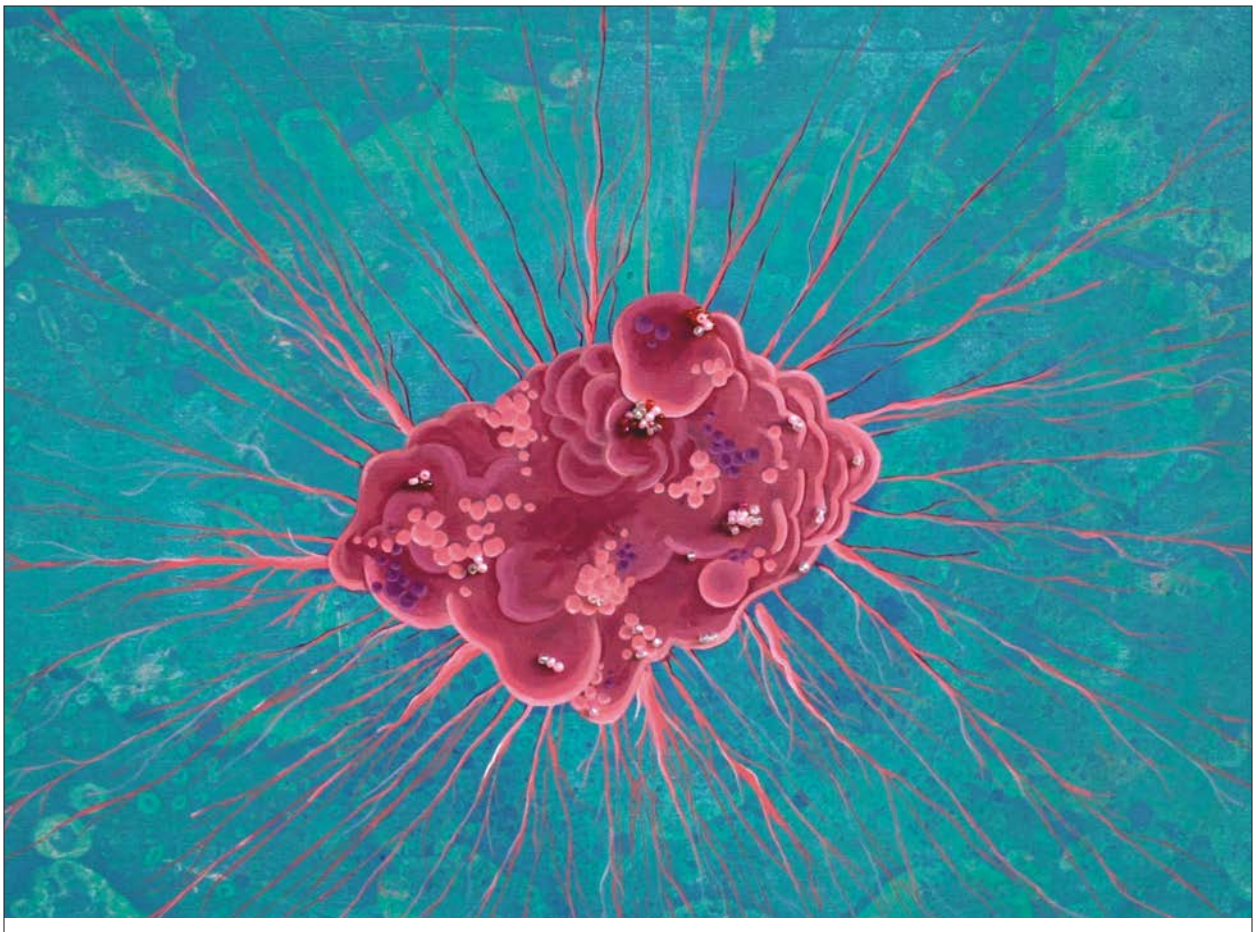

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Current Drugs Available Now for Interleukin-6 Suppression as Treatment Adjunct in Glioblastoma: Anakinra, Aprepitant, Mirtazapine and Olanzapine

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Abstract: Glioblastoma is a particularly aggressive cancer for which there are no good treatments as of autumn 2005. Mortality several years after diagnosis approaches 100%. This research summarizes evidence that a) most glioblastomas synthesize and secrete interleukin-6, b) that interleukin-6 is a significant growth and survival factor for these cells and c) that glioblastoma cells are stimulated to increase their interleukin-6 production by histamine acting on H1 receptors or by constitutive H1 receptor activity even in absence of ligand (histamine). New and unusually potent antihistamines (inverse agonists) are currently on the market (mirtazapine, olanzapine). Other less potent H1 antihistamines have been shown to inhibit interleukin-6 synthesis in other cell systems *in vitro* and when used clinically in humans in the upper airway. Mirtazapine and olanzapine inhibit both constitutive and ligand stimulated H1 receptor activity. They might also thereby inhibit glioblastoma's interleukin-6 synthesis. By thus depriving glioblastoma of a growth factor these antihistamines may slow this ferocious cancer's growth. Substance P and interleukin-1 beta have been also shown to stimulate interleukin-6 synthesis in some systems. Aprepitant is an oral substance P antagonist on the market to treat nausea and vomiting of cancer chemotherapy and anakinra is a parenteral interleukin-1 inhibitor on the market to treat rheumatoid arthritis- it is suggested that these be given as well in the attempt to deprive glioblastomas of interleukin-6. There are other cancers that are partially driven by il-6 acting as a growth factor- for example colon cancer, melanoma, multiple myeloma and prostate cancer. If these drugs really do lower interleukin-6 levels and hence il-6 signaling, they should be tried in these cancers as well.

Key words: Anakinra, antihistamine, aprepitant, colon cancer, cytokines, glioblastoma, histamine, interleukin-6, melanoma, mirtazapine, myeloma, olanzapine, prostate cancer, substance P

Introduction

It's an ancient military maxim that 'amateurs study strategy and tactics, professionals study logistics, (Dunnigan, 1993). For amateurs read losers of war, for professionals read winners of war. Oncology, like the military aims at killing cells so to the degree that the maxim applies to oncology, for strategy and tactics read attacking the cancerous cells with antimetabolites, mutagens and cytotoxins, cytotoxic monoclonal antibodies and various tumor antigen vaccination strategies. For logistics read deprivation of growth factors and anti-neoangiogenesis maneuvers. This research aims

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at showing evidence that glioblastomas, GB, synthesize interleukin-6, il-6 and use il-6 as a growth factor. Evidence is reviewed that commonly used potent antihistamines may suppress il-6 synthesis. If so they should form part of an attack on the enemy's logistics and may thereby retard GB growth.

GB comprise about half of all primary CNS tumors with an incidence of 3.5/100,000/year (Ohgaki and Kleihues, 2005). GB is an aggressive cancer for which there are few treatment options beyond attempted thorough primary surgical resection (rarely achieved) and palliative radiotherapy and attempts at cytotoxic treatments (Gilbert and Loghin, 2005) usually resulting in small prolongation of life. Most patients are dead within a year or two of diagnosis (Ohgaki and Kleihues, 2005; Gilbert and Loghin, 2005). MRI imaging of GB shows unusual heterogeneity within and between patients and a shocking propensity recur at the original site or by extension to distant parts of the brain (Nelson, 2003). GB histology and pathologic classification are reviewed in Gudinaviciene *et al*. (2004), clinical behavior and surgical management in Hentschel and Lang (2003), MRI imaging in Nelson (2003) and intracellular signaling abnormalities in Konopa and Bonni (2003).

Interleukin-6, il-6, is a pleiotropic 26 kd cytokine (reviewed in Conti *et al*. (2002) and Heinrich *et al*. (2003) synthesized by various cells, notably mast cells, certain lymphocytes, monocytes, endothelial cells, neurons and most relevantly here, GB cells. Oddly, the anterior pituitary synthesizes il-6 too. Il-6 has long been recognized as a B lymphocyte differentiation factor (and originally termed such) (Jego *et al*., 2003; Tackey *et al*., 2004)) and an osteoclast differentiation factor that is for example up regulated in and central to the bone lesions of Paget's disease (Reddy *et al*., 1999). Il-6 is seen to be up regulated at the site of bone resorption of various etiologies (O'Keefe *et al*., 1997), particularly the lytic lesions of multiple myeloma (Gado *et al*., 2000).

Il-6 is recognized as a differentiation factor for glia, for example C6 glioma cells are induced *in vitro* to differentiate into astrocytes by il-6 (Takanaga *et al*., 2004). Common neural stem cells (precursor to neurons, astrocytes and oligodendrocytes) differentiate to astrocytes after exposure to il-6 (Nakashima and Taga, 2002). Transgenic il-6 over-expressing mice show impaired neurogenesis (Vallieres *et al*., 2002), the common neural stem cell seeming to be diverted to glia formation in these mice. Over the last century there have been expressed recurring suspicions of a tenuous association of GB developing after and at the site of previous, often decades remote, traumatic brain injury (Moorthy and Rajshekhar, 2004). Elevation of il-6 is seen in cerebrospinal fluid and at sites of CNS neurotrauma or brain tear (Holmin and Hogeber (2004) for example, the locally up regulated il-6 providing a chronic glial stimulus leading to malignant transformation at some point.

This study documents evidence that GB synthesizes and uses il-6 as an autocrine growth factor. Published research data collected over the last decade is presented indicating that several easy-to-use, benign, drugs currently on the market are suppressive of il-6 synthesis in non-GB situations, *in vitro* and *in vivo*. The current paper attempts to give a full account of the data base linking H1 antihistamines to il-6 lowering. Various fragments of this story have been briefly presented (Altschuler and Kast, 2005a, b; Kast and Altschuler, 2004). By using potent H1 antihistamines, we might be able to inhibit GB's synthesis and use of il-6 and thereby deprive the tumor of one of its required growth factors. Deprived of il-6 signaling, disease progression may be retarded. The treatment method of this paper is not suggested with curative intent, nor to replace standard current treatment efforts. The il-6 suppressive medicines are suggested in the hope of retardation of growth and prolongation of life.

GB probably uses many paths to stimulate il-6 and il-6 is probably only one of many growth stimulating factors. Potent H1 antihistamines are suggested because a) we have many decades of experience with their use, b) the side effect profile is benign and in the case specifically of olanzapine and/or mirtazapine often salutary in terminal illness anyway and c) we have little to offer patients with GB and every little bit of growth retardation might be welcome.

The psychotropic drug olanzapine (Zyprexa) has been on the market for several years and is in widespread use in psychiatry to treat bipolar disorder, schizophrenia and as augmentation in the treatment of resistant depression, although only the first two indications are FDA approved uses in USA. It is an extraordinarily strong antihistamine at the H 1 receptor. Quetiapine (Seroquel), another antihistamine psychotropic on the market was suggested previously for use in multiple myeloma to lower il-6 levels and thereby deprive myeloma cells of a required growth factor (Kast and Altschuler, 2004). The current paper extends this suggested role of antihistamines for lowering il-6 using olanzapine and/or mirtazapine. These latter two drugs might be preferable to quetiapine for lowering il-6 by virtue of their strong antagonism at the serotonergic 5-HT2A receptor as well, a quality where quetiapine is weak. This will be explained later.

GB Secrete Interleukin-6

Here is the evidence GB often secrete pathologically significant elevated levels of il-6: Cerebrospinal fluid il-6 was increased in 11 of 13 GB patients (van Meir *et al*., 1990). Frozen sections of aggressive anaplastic GB were more active in il-6 synthesis than were sections from less aggressive GB (Giometto *et al*., 1996). Others found immunohistochemically demonstrable il-6 in 15 of 20 GB sections (van Meir *et al*., 1990). Primary *ex vivo* human GB examined for il-6mRNA were positive in 86% of cases (Huettner *et al*., 1995). Most primary explants of human GB synthesized il-6 (Lichtor and Libermann, 1994).

Human GB cell line G5 synthesizes il-6 and this il-6 was related to its radioresistance (Dubost *et al*., 2002). GB tissue contain more il-6 than control brain (Choi *et al*., 2002). Half of excised human GB were immunohistochemically il-6 positive (Sasaki *et al*., 2001). Aggressiveness of human GB correlated with degree of up regulation of il-6 (Tchirkov *et al*., 2001). Various GB cell lines synthesize il-6 (23, Falus, 1993; Goswami *et al*., 1990; Hotfilder *et al*., 2000; Kiriyama *et al*., 1997). Human GB biopsy tissue showed both il-6 and the il-6 receptor (il-6R) (Goswami *et al*., 1998). Antibodies to il-6 suppressed *in vitro* growth of a GB cell line (Goswami *et al*., 1998).

Histamine Stimulates Interleukin-6 Synthesis

Here is the evidence suggesting histamine acting through the H1 receptor can stimulate il-6 synthesis and H1 antihistamines suppress il-6 synthesis.

Histamine, a phylogenetically ancient neurotransmitter, is synthesized from histidine by histidine decarboxylase. It signals by binding to the active form of its cognate cell surface receptor. Of the several types of histamine receptors, H1 and H2 are the most common, H1 the most widely expressed throughout the body.

There is reason to think that mirtazapine and olanzapine may be particularly felicitous antihistamines in lowering il-6. Upon histamine binding to H1, prominent intracellular events are phospholipase C activation with consequent formation of inositol 1, 4, 5 triphosphate and diacylglycerol and activation of signaling pathways secondary to these second tier second messengers. Other phospholipases (D and A2) and nuclear factor kappa B, NFkB, activation can also be seen after H1 receptor activation (Leurs *et al*., 2002; MacGlashan, 2003). Since both olanzapine and mirtazapine have strong antagonism at the 5-HT2A serotonergic receptor and 5-HT2A activation results in phospholipase C activation as well (Barnes and Sharpe, 1999), it is possible 5-HT2A antagonism that mirtazapine and olanzapine provide will be intracellularly additive to the H1 blockade as far as intracellular consequences go and thereby further and more potently suppress il-6.

Note that the H1 receptor has some intrinsic, constitutive activity- intracellular signaling even in absence of ligand. H1 receptor shuttles back and forth between active and inactive state. Agonist ligands like histamine lock the receptor (tends to retain the shuttling receptor for longer time) in the active state, inverse agonists (like all the antihistamines discussed in this research) tend to lock the

receptor in the inactive state. Therefore the inverse agonists suggested in this research- olanzapine and mirtazapine have the potential to lower H1 functions even in the absence of histamine or any agonist signaling. Throughout this discussion the term antihistamine is used, but formally inverse agonist would be the correct term.

Prominent histamine producers are gastric parietal cells, mast cells, basophils and neurons (cell bodies of these neurons are located exclusively in the tuberomammilary nucleus of the posterior hypothalamus although dendrites of these neurons project to and release histamine throughout the cortex). Outlined below are several other cell types synthesizing histamine. Here is the evidence histamine stimulates il-6 synthesis:

In vivo

Common currently marketed oral H1 antihistamines mizolastine and fexofenadine (Allegra) significantly lowered il-6 content of nasal washing fluid in allergic rhinitis patients challenged by allergen (Ciprandi *et al*., 2004). Il-6 induction is diffusely and generally impaired in histamine deaminase deficient (and hence histamine deficient) mice (Horvath *et al*., 2002).

In vitro

The H1 antagonist azelastine (Optivar) inhibited il-6 release from cultured human umbilical cord derived mast cells stimulated by IgE (Kempuraj *et al*., 2003). Human umbilical cord endothelium cells synthesized il-6 when stimulated by histamine that was inhibited by H1 specific anti-histamine desloratadine (Clarinex) (Molet *et al*., 1997). Cultured human mast cells synthesized il-6 and this was largely inhibited by the H1 antagonists azelastine and olopatadine (Patanol) (Kempuraj *et al*., 2002, 2003). Azelastine inhibited il-6 synthesis of fresh human peripheral blood lymphocytes (Yoneda *et al*., 1997). Free histamine induced il-6 synthesis and release by human kertainocytes and this was inhibited by H1 antagonist emedastine (Kohda *et al*., 2002). Human coronary artery endothelial cells cultured *in vitro* showed il-6 ineducability by histamine that was synergestic with lipopolysaccharide or tumor necrosis factor-alpha, TNF-alpha (Li *et al*., 2001). Human purified lung parenchyma macrophages showed il-6 synthesis induction after histamine addition that was inhibited be fexofenadine (Marone *et al*., 2001). Nannomolar concentrations of histamine increased otherwise unstimulated basal synthesis of il-6 in human lung macrophages that was inhibited by fexofenadine (Triggiani *et al*., 2001). Primary cultures of human conjunctival epithelial cells secreted il-6 after stimulation by histamine that was inhibited by the H1 inhibitors emedastine (Weimer *et al*., 1998; Yanni *et al*., 1999) and antazoline, olopatadine and pheniramine (Yanni *et al*., 1999). (Pheniramine is widely available and used without prescription in USA in various remedies for upper respiratory infections). Human bronchial epithelium were stimulated to make il-6 by histamine (Takizawa *et al*., 1995). Of specific interest to the thesis developed in this paper, histamine stimulated il-6 synthesis in various GB cell lines *in vitro* (Falus, 1993).

Histamine augmented ultraviolet induced il-6 synthesis in cultured human keratinocytes that was blocked by the H1 antagonist pyrilamine (Shinoda *et al*., 1998) (widely available and used without prescription). Il-6 protein and mRNA increased after histamine in bone marrow stroma cells (Takamatsu *et al*., 1998). Gingival fibroblasts and peripheral blood lymphocytes and monocytes showed decreased il-6 synthesis after azelastine. Peripheral blood mononuclear cells synthesized il-6 after histamine (Mor *et al*., 1995). A mast cell line and a basophil cell line showed decreased il-6 synthesis after desloratadine (Lippert *et al*., 1995).

Other Stimuli for Interleukin-6 Synthesis

There are no doubt multiple growth factors in addition to il-6 and il-6 probably has multiple redundant paths for its stimulation in GB. There are however two other systems implicated in il-6 stimulation for which, like H1 antihistamines, there happen to be drugs already on the market to inhibit.

Here is evidence for three such other il-6 stimulating receptor systems:

Substance P, SP, (synonym is neurokinin-1) is a secondary stimuli for il-6 synthesis. SP is an eleven amino acid peptide neurotransmitter, secreted by eosinophils, endothelial cells, macrophages as well as neurons throughout the brain and spinal cord (O'Connor *et al*., 2004). SP is considered a stimulatory late acting B lymphocyte differentiation factor with wide ranging developmental effects on bone marrow lymphocytes (Kang *et al*., 2004). SP signals through phospholipase C activation as does H1 receptor, with rapid post ligation formation of inositol 1, 4, 5 triphosphate and diacylglycerol (Cavelier *et al*., 2004). Astrocytes bear SP cognate receptors and SP stimulates il-6 in human astrocytoma cells (Cadman *et al*., 1994; Lieb *et al*., 1998).

Interleukin-1 beta, il-1 beta is also seen to be a stimulus for il-6 synthesis. Il-1 beta is a 17 kd cytokine synthesized by primarily be monocytes and monocytes lineage cells like macrophages (il-1 beta reviewed in Dinarello, 2002) with multiple functions in directing immune responses. Il-1 beta is normally expressed at low level but is rapidly upregulated at time and place of inflammation. Il-1 beta was seen to stimulate il-6 in a human astrocytoma cell line (Cadman *et al*., 1994; Lieb *et al*., 1998) and in a glioma cell lines (Spangelo *et al*., 2000, Spangelo *et al*., 2004) and cultured gut epithelial cells (Parikh *et al*., 1997). Il-1beta stimulates synthesis and release of il-6 from anterior pituitary cells and other cells as well (Shinoda *et al*., 1998; Spangelo *et al*., 2000). There is evidence that this specific il-6 stimulatory pathway is active in GB: seventy percent of human surgically excised GB are immunohistochemical positive for il-1 beta (Sasaki *et al*., 2001). In several *in vitro* systems, il-1 beta stimulated il-6 synthesis and release from GB cell lines (Kiriyama *et al*., 1997; Spangelo *et al*., 2000, 2004).

Of interest and potential significance is the recent observation that, although il-1 beta receptors have been considered to be positively coupled to adenylate cyclase (il-1 beta binding increases adenylate cyclase activity) phospholipse activation is required for certain proliferation related responses to il- 1 beta (Amin *et al*., 2003) a feature in common with H1 and SP receptors.

Agonists acting on the 5-HT7 receptor have been shown just this year to stimulate il-6 production in a human microglia cell line (Mahe *et al*., 2005) and a human astrocytoma cell line (Lieb *et al*., 2005).

The Suggested Drugs

Mirtazapine

A unique antidepressant and potent H1 antihistamine, mirtazapine is also a potent antagonist at 5-HT3 (de Boer *et al*., 1988; de Boer, 1996; Fawcett and Barkin, 1998). Mirtazapine shows correspondingly strong anti-nausea effects. Mirtazapine is used in the latter role as treatment of cancer chemotherapy related nausea and vomiting (Kast, 2001). Mirtazapine increases TNF (Kast, 2003) and probably does that by Gi protein negative coupling to adenylate cyclase. The net neuronal effect of mirtazapine is increased signaling at the serotonin 5-HT1A receptor (de Boer *et al*., 1988; deBoer, 1996; Fawcett and Barkin, 1998) and 5-HT1A is negatively coupled to adenylate cyclase (Barnes and Sharp, 1999). Adenylate cyclase is the enzyme converting adenosine triphosphate to cyclic adenosine monophosphate, cAMP. Since il-6 and TNF tend to be inversely regulated (findings reported in Grandjean-Laquerriere *et al*. (2003) typical of many) this is further ground for suspecting mirtazapine will lower il-6. Since mirtazapine probably increases TNF by decreasing intracellular cAMP, it should therefore decrease il-6. Il-6 synthesis tends to be regulated by direct relationship to intracellular cAMP (15, Granjean-Laquerriere *et al*., 2003; Riminucci *et al*., 2003) are typical findings among many) while TNF tends to be regulated by an inverse relationship to intracellular cAMP levels (Kast, 2000). Mirtazapine is also a strong serotonergic antagonist at the 5-HT2A receptor which may well synergize with its antihistamine effects as outlined above. Serotonin stimulated inositol 1, 4, 5 triphosphate generation was abolished by mirtazapine *in vitro* (Millan *et al*., 2000).

Olanzapine

Olanzapine is one of the most potent H1 antihistamines on the market. A mood stabilizing psychiatric drug with significant antidepressant and anti-psychotic effects and multiple receptor bindings and antagonisms (Bymaster *et al*., 1996, 1999; Bymaster *et al*., 2001), it is approved for use in treatment of bipolar disorder and schizophrenia. It is also commonly used by psychiatrists in augmentation role in treatment of severe or treatment resistant depression. Olanzapine has potent anti-nausea effects, probably by virtue of its strong antagonism at the 5-HT3 receptor (Bymaster *et al*., 2001) as for mirtazapine and the standard 'setron class (ondansetron, granisetron, etc.) anti-emetics. Note that strong 5-HT3 antagonism has been noted to suppress SP synthesis (Stratz *et al*., 2004). Olanzapine is also used in cancer chemotherapy nausea control (Davis *et al*., 2002; Editorial, 2003). Olanzapine has significant antagonism at the 5-HT2A receptor which may act synergistically with anti-H1 effects as mentioned. Olanzapine has little propensity to induce parkinsonian effects or akathesia and is easy to use in the non-psychiatric population. Its prominent side effect is increased appetite which might not be adversive in the proposed patient population.

Olanzapine may be particularly well suited to a treatment trial in GB because it has been found also to be an antagonist at 5-HT7 receptors (Thomas *et al*., 1998). There is evidence that olanzapine is actually functioning there as an inverse agonist which is even better in that constitutive activity in absence of ligant would thus be inhibited as well.

Anakinra

A commercially available 17 kd recombinant non-glycosylated form of il-1 Ra, anakinra (Kineret) is given by subcutaneous injection one or more times a day. Il-1Ra is a circulating 152 amino acid inhibitor of il-1 beta function. By binding but not activating the il-1 receptor, il-1Ra prevents that receptor's activation by il-1 beta. Approved for use in USA and EU for treatment of rheumatoid arthritis, it has a benign side effect profile (Kay and Galabrese, 2004). Its suggested use in GB is to bind to the il-1 receptor and thereby prevent il-1 beta stimulation of il-6 synthesis by GB or the GB stroma or the GB infiltrating mononuclear cells (monocytes, lymphocytes).

Aprepitant

Substance P is kd 11 amino acid peptide neurotransmitter (Herpfer and Lieb, 2005). Receptors for SP are found on neurons and glia throughout the brain (Herpfer and Lieb, 2005) and in particularly high concentration on GB cells Yamaguci *et al*. (2005). An orally administered specific SP antagonist on the market several years now, aprepitant (Emend) is used for reduction of cancer chemotherapy related nausea and vomiting (Navai, 2004). Greater than 90% of brain SP receptors are occupied (blocked) by usual clinical doses (Bergstrom *et al*., 2004). It has a benign side effect profile and probably has antidepressant effects (Herpfer and Lieb, 2005; Blier *et al*., 2004). Since evidence cited above indicates some il-6 may be stimulated by SP aprepitant should be added to further suppress il-6. An intriguing dovetail observation is lowering of circulating SP in fibromyalgia patients by 5-HT3 sertonergic antagonists of the setron class (granisetron, ondansetron and others) (Stratz *et al*., 2004). Both mirtazapine and olanzapine have potent antagonism at 5-HT3 receptors as discussed above so they may lower SP as well.

Empirically, SP receptor blockers other than aprepitant have been shown to block GB cell lines' growth *in vitro* (Yamaguci *et al*., 2005).

Discussion

Il-6 is synthesized by GB cells and functions as an autocrine growth factor for them. In other cell systems, histamine stimulates il-6 synthesis via H 1 receptors and there is some evidence it may do so in GB. H 1 antihistamines suppress il-6 synthesis in several cell systems. Mirtazapine and

olanzapine are extraordinarily potent antihistamines active at H 1 and may lower il-6 in GB and may thereby retard GB growth. Other binding attributes of mirtazapine and olanzapine may make them particularly well suited as il-6 lowering agents.

GB cells may not be unique in using il-6 as a growth factor important to malignant growth. Il-6 has been implicated as a significant growth factor in other cancers as well in part by virtue of its attribute termed promiscuous. An example of this attribute is prostate cancer where il-6 is believed to be a major escape path from androgen dependency in hormone refractory prostate cancer progression after castration (Corcoran, 2003; Culig, 2003). Androgen receptors remain in this situation almost universally expressed yet the malignant cells continue to flourish without androgen. Il-6 ligation to the androgen receptor causes half maximal stimulation of that receptor in the absence of any androgen (Corcoran, 2003; Culig, 2003) and is believed to thus provide growth stimulus at the androgen receptor without androgen. Empirically, sharp rises in il-6 preceded prostate specific antigen (PSA) rise and precede clinical evidence of progression (Culig, 2003).

II-6 levels are elevated in and correlate to poorer prognosis, shorter survival, in renal cell carcinoma (Negrier *et al*., 2004), breast cancer (Bachelot *et al*., 2003; Salgado *et al*., 2003), colon cancer (Chung and Chang, 2003; Miki *et al*., 2004) and malignant melanoma (Soubrane *et al*., 2005; Mouawad *et al*., 2002). Circulating il-6 levels are elevated in gastric cancer (Galizia *et al*., 2002), pancreatic cancer (Ebrahimi *et al*., 2004), non-small cell lung cancer (McKeown *et al*., 2004) and hepatocellular carcinoma (Coskun *et al*., 2004) among others. Il-6 has also been mechanistically implicated in multiple myeloma (Gado *et al*., 2000) and melanoma (Soubrane *et al*., 2005; Mouwad *et al*., 2002). Melanoma cell synthesized histamine has been shown to be an autocrine drive to production of il-6 (Molnar *et al*., 2000).

In an *in vitro* model with colon cancer cells, addition of il-1RA prevented il-1beta mediated il-6 increases (Miki *et al*., 2004). The suggested system for il-6 suppression GB might well be tried in these cancers as well.

Anakinra, aprepitant, mirtazapine and/or olanzapine, should be tried in GB after primary maximal resection in a formal clinical study. These drugs should be considered in other cancers where il-6 is a growth factor.

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