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AS WE SEE IT

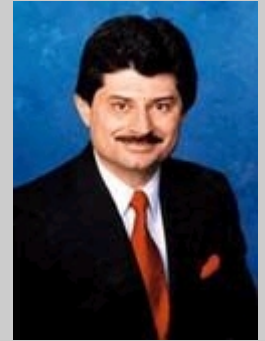
Science Versus Dogma

Cancer treatment breakthroughs frequently appear in scientific journals, yet victims of the disease are often denied access to these promising therapies. We at The Life Extension Foundation learned long ago that what is published in the peer-reviewed medical literature is seldom incorporated into clinical oncological practice. This means that cancer patients suffer and die while effective therapies already exist.

One reason for this treatment deficit is the complexity of administering multi-modal treatments that have to be tailored to the individual patient. For instance, few oncologists are conducting the advanced tumor cell gene tests that The Foundation advocated years ago.(1) These tests, when properly interpreted, enable someone with a background in molecular oncology to design an individual treatment protocol that kills most cancer cells, inhibits various growth phases of remaining tumor cells, and blocks the escape mechanisms that enable residual cancer cells to become resistant to cell cycle regulatory control. While the scientific literature provides a rationale for these multi-modal approaches, conventional oncology remains fixated on mono-therapeutic agents that have long ago been proven to fail.

It's not just lack of physician motivation that is causing the cancer carnage to occur. Large drug companies are hampered by FDA bureaucratic delays. The FDA's response to the outcries from desperate cancer patients is to offer "compassionate-use exemptions" for drugs that someday may be approved. Unfortunately, the cancer patient has to locate a physician willing to fill out an enormous amount of paperwork to qualify for compassionate-use exemption, and the drug company then has to be convinced to "give away" the unapproved drug. The FDA makes it illegal to sell an unapproved experimental drug and drug companies are not in the business of giving away their products. The result is that most terminal cancer patients are denied access to potential lifesaving drugs even though the FDA has this so-called "compassionate-use" policy in place.

Surprisingly, the inability to access a compassionate-use drug is not always that bad, since the FDA and drug companies often restrict the patient from using other drugs that would synergistically work with the experimental drug for which compassionate-use is being sought. The FDA and drug companies, you see, don't want to see their statistics skewed by a patient that might actually figure out a way of combining several approved and unapproved therapies in a way that could cure their disease. The FDA's view on human experimentation is to evaluate the effects of a single drug on a specific type of cancer. Since other therapies that may be synergistic are often disallowed, most cancer patients are left to suffer an excruciating death under the watchful eye of the oncologist overseeing the "compassionate-use" of the experimental drug. This oncologist then dutifully reports to the FDA and drug company every bit of agony suffered as the cancer slowly spreads through the patient's body.



William Faloon



Rescuing cancer patients

The Life Extension Foundation views the current state of experimental oncology as sadistic and barbaric. That is why so much effort is being made to open The Life Extension Medical Center in Ft. Lauderdale, Florida early next year. Based on the inadequacies of current medical practice, we feel it is critical for Foundation members to gain access to the latest state-of-the-art therapies in case they contract a lethal disease.

At The Life Extension Medical Center, physicians will be required to display an exceptional degree of motivation, compassion and creative molecular expertise. These front-line physicians will be backed by a team of researchers who will search the worldwide scientific literature and assist in designing optimal treatment protocols for each individual patient. Another unique component of The Life Extension Medical Center will be the lawyers who will sue the FDA and/or drug company when a potential life saving medicine is denied to a terminally ill human being.

The long-term objective of establishing The Life Extension Medical Center is to create an environment where science will prevail over dogma in a way that will revolutionize the practice of medicine in the United States. Our intent is to abolish the current "assembly line" form of clinical care that is causing so many people to die unnecessarily.

Why chemotherapy so often fails

Drugs that kill cancer cells are called "cytotoxic" chemotherapy agents. While chemotherapy drugs can play an important role in a comprehensive treatment program, there are escape mechanisms whereby cancer cells become resistant to cytotoxic agents. An alternative to using only cytotoxic drugs is to add other agents that work synergistically with conventional chemotherapy to eradicate cancer cells.

Many cancers proliferate out of control because of certain growth factors that make them resistant to conventional (and alternative) cancer therapies. One of these factors, called "transforming growth factor," binds to a receptor site on cancer cells called the "epidermal growth factor receptor." The binding of "transforming growth factor" to these cancer cell "receptors" creates a signal that induces rapid cell division, resulting in aggressive disease and poor prognosis.

There are drugs that block the "epidermal growth factor receptor," thus interfering with the ability of "transforming growth factor" to signal cancer cells to propagate out of control. These drugs are not toxic chemotherapy agents, but instead are classified as "cytostatic" drugs, in as much as they directly inhibit signal-induced hyper-proliferation of cancer cells. These drugs are in clinical trials and are not yet available to most cancer patients.

Drug denied to cancer patients

One example of a promising therapy bogged down in the FDA's regulatory quagmire is a drug called Iressa, made by the pharmaceutical giant AstraZeneca. The encouraging results from clinical studies on Iressa has caused many terminal cancer patients to seek "compassionate-use" exemption from the FDA. Unfortunately, few cancer patients meet the exacting standards needed to qualify for "compassionate-use." The result is that tens of thousands of cancer patients are dying right now waiting for FDA approval. A somewhat technical description of the molecular mechanisms by which Iressa works to suppress cancer cell growth can be found at the end of this article.

Reducing chemotherapy side effects

The toxic side effects of conventional chemotherapy can be so severe that the patient is often unable to tolerate a dose adequate to kill enough of the cancer cells, or the patient may die from the chemotherapy itself. There are proven ways to protect against the side effects of cytotoxic therapy. Unfortunately, oncologists often fail to prescribe these agents that protect against chemotherapy-induced toxicity, even though some of them are FDA-approved drugs. It should also be noted that in many cases, the patient's HMO refuses to pay for these drugs that protect against chemotherapy-induced toxicity. This means that cancer patients needlessly suffer and die because of inadequate drug management.

The Life Extension Foundation has previously published protocols on some of the drugs that are approved by the FDA to protect against some of the side effects of cytotoxic chemotherapy drugs. These protocols can be accessed at the Foundation's website (www.lef.org) or in the 946-page Disease Prevention and Treatment reference book.

The FDA and drug companies don't want to see their statistics skewed by a patient that might actually figure out a way of combining several approved and unapproved therapies in a way that could cure their disease.



Failing to prescribe FDA approved drugs

There are drugs approved by the FDA to treat other diseases that also inhibit tumor cell growth. While it is legal for doctors to prescribe these drugs for "off-label" uses, the FDA makes it illegal for drug companies to promote them for "off-label" uses, such as adjunctive cancer therapy.

Some of these drugs, such as the COX-2 inhibitors and "statins," have been recommended by The Life Extension Foundation for years, but many cancer patients have not been able to convince their oncologist to prescribe them. The Life Extension Medical Center will be committed to incorporating into each patient's treatment regimen every therapy that is supported in the peer-reviewed scientific literature as having efficacy against their particular serious disease. A review of The Foundation's protocols for using some of these off-label drugs as adjunctive cancer therapies can be found at www.lef.org or in the book, Disease Prevention and Treatment.

Escaping from the abyss

For 20 years, The Life Extension Foundation has published specific recommendations on what people with lethal diseases can do to improve their chances of surviving. We are confident that tens of thousands of lives have been saved by our efforts, but we also fear an equal number of people were unable to secure physician cooperation and succumbed to their disease.

At The Life Extension Medical Center, patients will be assured that every possible treatment modality with demonstrated efficacy will be used in a synergistic and aggressive attempt to eradicate their disease.

It is our opinion that to radically change the way medicine is practiced, someone will have to lead by example. The Life Extension Medical Center intends to set that example. The costs of constructing the initial medical facility and staffing it with top-flight medical personnel is enormous. Members should feel gratified that their product purchases are helping to finance the pioneering physicians and researchers who have dedicated their professions to making the practice of medicine a purely scientific endeavor, as opposed to the dogmatic ritual that currently exists.

The successes enjoyed by The Life Extension Foundation this year in persuading Congress to legalize the importation of lower cost medications from other countries should make implementing these multi-modal approaches to cancer treatment more affordable. Our goal in the year 2001 will be to convince Congress to pass legislation to allow terminally ill patients to gain much greater expanded access to promising experimental therapies.

The Life Extension Foundation is battling the entrenched medical establishment on many fronts. Your support of our efforts through the purchase of supplements designed to reduce your risk of contracting these horrendous diseases will make a huge impact on the betterment of mankind.

For longer life,



William Faloon
Life Extension Foundation

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1. IMPATH Laboratories offers the immunohistochemistry tumor cell test that reveals what therapeutic agents are most likely to succeed. They can be reached at 1-800-447-5816.

FOLLOW UP:

Life Extension Technical Report: Suppressing cancer cell growth - a novel approach

AS WE SEE IT

LIFE EXTENSION TECHNICAL REPORT:

Suppressing cancer cell growth - a novel approach

Some readers may find this section somewhat technical, but it provides a stark example of how important it is to treat cancer patients along the revolutionary guidelines being proposed by The Life Extension Foundation.

How to make chemotherapy drugs work better

It has been established that “transforming growth factor” causes rapid cancer cell proliferation when it binds to the “epidermal growth factor receptor.” Overexpression of the “epidermal growth factor receptor” has been found in tumor cells that are resistant to cytotoxic drugs.

Iressa is classified as an “epidermal growth factor receptor inhibitor” that blocks signal transduction pathways implicated in cancer cell proliferation and other processes promoting cancer growth. One recent study(1) showed that Iressa induced a dose-dependent two- to four-fold increase in apoptosis (cell death) in all cancer cell lines tested. Iressa’s primary mechanism is to induce cell cycle arrest in the G1 phase. When Iressa was combined with various cytotoxic drugs (such as Taxol, cisplatin, carboplatin, Adriamycin), a supra-additive, growth inhibitory effect was observed on all doses.

This study showed that when human colon adenocarcinoma cell lines are transplanted into immunodeficient mice, Iressa suppressed tumor cell growth and significantly increased survival in the highest dose. Iressa functioned as a cytostatic, rather than cytotoxic agent, though an increase in programmed cell death (apoptosis) in higher doses was observed. When combined with cytotoxic drugs, Iressa induced a significant suppression of tumor growth as compared to untreated controls or to single agent-treated mice. The delayed growth observed in animals receiving Iressa plus cytotoxic therapy was accompanied by prolonged life span of mice that was significantly greater than untreated controls or single agent-treated animals. In one group treated with the cytotoxic drug Taxol plus Iressa, 40% of the mice were still alive 16 weeks after tumor injection (the only group to survive this long). Combined treatment did not induce signs of toxicity. Iressa thus demonstrated in vivo antitumor activity in immunodeficient mice with established tumor xenografts.

In the colon cancer test groups, the tumors in the untreated controls reached a size not compatible with normal life within four to six weeks after cell injection. In the single-agent group, tumor reached terminal size within six to eight weeks after cell injection. In contrast, in those animals receiving combination therapy (Iressa plus the cytotoxic drug), 50% of the animal were alive 10,12 and 15 weeks after cancer cell injection.

The scientists conducting this study speculated that in an attempt to increase survival and possibly eradicate established tumors, that additional cycles of combination Iressa and cytotoxic drug therapy could be administered. It was also noted that the mechanisms of action of Iressa seemed to be different than those of chemotherapy drugs used in combination. Iressa was shown to produce an enhanced effect when used with chemotherapy drugs that exert their cytotoxic effect via different structural mechanisms.

The results of this study are consistent with previous reports showing that a synergistic effect in the arrest of tumor growth when cytotoxic drugs are combined with an agent that blocks epidermal growth factor receptors such as Iressa. The beneficial mechanism postulated by the scientists who conducted this study is that cellular damage by chemotherapy can convert epidermal growth factor receptor ligands into survival factors for those cancer cells that express the epidermal growth factor receptor, ergo a reason why chemotherapy drugs often fail to induce long-term survival in the clinical setting. By blocking the epidermal growth factor receptor signaling pathway and other cell cycle growth factors, Iressa used in combination with cytotoxic drugs could cause irreparable cell damage, leading to the desired programmed cell death (apoptosis) of cancer cells.

In the clinical setting, the potentiation of the antitumor activity of cytotoxic drugs by interfering with epidermal growth factor receptor activation may make possible a reduction in the dose of chemotherapy drugs that normally cause systemic harm to the host. It may thus be possible to use Iressa to reduce the amount of toxic chemotherapy drug needed to achieve remission, and over a longer period of time, use Iressa to induce cancer cell apoptosis.

Iressa monotherapy

In order to ascertain the safety and efficacy of Iressa monotherapy, a study was conducted at four major cancer centers on a group of 58 patients with advanced disease. Ten of these patients had advanced head and neck cancers. In three out of nine head and neck cancer patients treated with low-dose Iressa (150 mg/day), a 20% reduction in tumor reduction occurred, with a 60% visual reduction of a large lip tumor and decreases in dermal metastasis. The conclusion of this study was that Iressa had acceptable tolerability, and produced antitumor activity when given as monotherapy. The findings of this study were presented at a cancer conference held last year.(2)

Iressa's multiple mechanisms of action

According to a presentation published at a recent cancer conference,(3) the drug Iressa functions as a specific epidermal growth factor receptor tyrosine kinase inhibitor. The researchers stated that Iressa has demonstrated powerful antitumor activity both in vitro and in vivo and pointed to the following specific mechanisms of action to describe the drug's antitumor effects:

- Iressa induced growth arrest of head-neck squamous cell carcinomas by inhibiting epidermal growth factor mediated cell signaling.
- Iressa induced a delay in cell cycle progression.
- Iressa induced a complete arrest of G1 phase cell growth after 72 hours of treatment.
- Iressa induced a time-dependent upregulation of the p27 cyclin-dependent kinase inhibitor.
- Iressa induced a dose-dependent decrease in cyclin-dependent kinase 2 activity within 24 hours of treatment.

These investigators noted that the combined effects of upregulating p27 and decreasing cyclin-dependent kinase 2 shed new light on how Iressa could favorably regulate cell-cycle machinery via growth factor receptor mediated signal transduction pathways, leading to further cell growth arrest.

Iressa in the treatment of squamous cell carcinoma

Treatment of squamous cell carcinoma by interferon-alpha has been successfully demonstrated.(4-8) At some point in the treatment, however, the tumor becomes refractory to the inhibitory effects of interferon and propagates out of control.(9)

Squamous cell carcinomas often exhibit an overexpression of the epidermal growth factor receptor.(10-12) Since upregulation of epidermal growth factor receptor is an escape mechanism to the antitumor effect of interferon-alpha, the concomitant use of the drug Iressa, which specifically blocks tyrosine kinase—the enzyme responsible for activating the epidermal growth factor receptor—appears to be a logical therapeutic approach to be used in cases where the primary squamous cell carcinoma has been significantly de-bulked using cytotoxic therapies, and the ultimate treatment objective is eradication of residual tumor using biological response modifiers like interferon-alpha.

Squamous cell cancers are often associated with high level overexpression of epidermal growth factor receptor, and therefore present a novel opportunity to use agents like Iressa in combination with proven biological response modifiers such as interferon-alpha, which have been shown to synergistically arrest cell growth. Investigators have proposed that the combined effects of Iressa and interferon-alpha on the induction of cancer cell growth arrest and apoptosis (programmed cancer cell death) is synergistic, and recommended that these two drugs (Iressa and interferon-alpha) be combined in a clinical study of advanced squamous cell carcinomas that are “epidermal growth factor receptor” positive as determined by The Foundation's recommended cancer cell gene tests.(13)

A natural approach

Some Life Extension Foundation researchers have pointed to studies indicating that the herbal supplement curcumin also functions as an “epidermal growth factor receptor inhibitor.”(14-17) While these published studies are intriguing, especially as it relates to curcumin's ability to prevent cancer, the Life Extension Foundation prefers to continue battling the establishment to allow cancer patients to immediately access drugs like Iressa that are supported by actual human clinical cancer trials.

Conclusion

Scientists have published results using Iressa alone and in combination with cytotoxic drugs that provide a rationale for Iressa to be prescribed in cancer patients with epithelial tumors that express functional epidermal growth factor receptors. The preliminary results from two Phase I studies demonstrate that Iressa may be administered over a prolonged period to cancer patients in doses sufficient to produce positive biological effectiveness with no major toxic effects.

Interferon-alpha has demonstrated efficacy in controlling squamous cell carcinomas, but interferon also induces epidermal growth

factor, thus enabling cells overexpressing epidermal growth factor receptor to escape the antitumor effect of interferon-alpha.

In the in vivo model, Iressa and interferon have been shown to be synergistic, whereas combinations of cytotoxic drugs with Iressa are supra-additive. Thus, combining Iressa with the biological response modifier interferon-alpha, and/or cytotoxic chemotherapeutic agents, depending on the type of tumor involved, provides a practical opportunity to gain control over a particular cancer that would normally have a poor response rate.

Currently, clinical studies on Iressa are only planned for non-small cell lung cancer patients. To inquire about participating in these and possibly other studies, call AstraZeneca at 1-800-236-9933 or the Iressa expanded access program at 1-877-792-0518.

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