

# Avemar outshines new cancer 'breakthrough' drug

*by Michael Traub*

Many of us in the cancer research community were happy to hear about progress against metastatic melanoma reported this June at the annual meeting of the American Society of Clinical Oncology (ASCO). At least, we were happy at first.

After all, most naturopathic physicians realize that we will often see patients with cancer who have used or are using conventional therapies. And any advance is welcome in treating a disease for which there has not been an improvement in overall survival from chemotherapy in over three decades.

Data from a phase III clinical trial of the experimental monoclonal antibody ipilimumab (pronounced "ep-eh-lim-ue-mab") showed that patients with metastatic melanoma survived longer if they were taking ipilimumab than if they were not, regardless of whether they also were taking the other drug in the study, an experimental cancer vaccine. (1)

A Closer Look: How Big an Improvement, at What Cost to Patients?

But the enthusiasm initially generated by the "late-breaking" news at the ASCO news conference has caused some doctors,

patients, and others who work with complementary cancer therapies to look at results from similar clinical studies and wonder if this latest ipilimumab study is really the "breakthrough" that it's claimed to be.

### Overall Survival: the 'Gold Standard' for Judging Cancer Therapies

Overall survival (OS) is the length of time that a patient actually survives a cancer after treatment. It can also be measured as the percentage of patients surviving a specific time. It is the gold standard by which the usefulness of a cancer treatment should be determined. Many things can help a patient, but the most important goal of doctors and patients is for the cancer patient to live longer, with a decent quality of life (QOL).

Among patients taking ipilimumab with or without the experimental vaccine, median overall survival was about 10 months. That is compared with 6.4 months' overall survival among patients receiving the vaccine by itself.

About 45.6% of patients taking ipilimumab survived one year, an improvement of some 7% over the 38% seen in some earlier studies.

This very modest improvement in survival comes at quite a price.

### Severe Side Effects in More Than One in Four Ipilimumab Patients

Ipilimumab has some side effects that can be "both severe and long-lasting," according to the study report.

Among patients taking ipilimumab by itself (without the vaccine), 19.1% had side effects requiring hospitalization or invasive intervention, 3.8% died from the effects of the drug, and another

3.8% had life-threatening or disabling side effects.

All totaled, 26.7% of the patients taking ipilimumab by itself-- more than 1 in 4--had side effects that were severe, very severe, or fatal. Severe side effects included diarrhea, nausea, constipation, vomiting, abdominal pain, fatigue, cough, and headache.

Vernon Sondak, MD, of the H. Lee Moffitt Cancer and Research Institute, said that "using the drug requires the medical team to be on guard to manage toxicity at all times."

But even with its severe side effects, the researchers said that the drug should be welcomed because it can increase median survival from 6.4 months to 10.1 months. That is because any lengthening of lives is welcome in a disease that hasn't seen a new drug that can do that in many years.

Fermented Wheat Germ (Avemar) Improves Melanoma Survival Without Harsh Side Effects

But what if there already were such a treatment available--not a drug, but a safe, natural substance shown in clinical trials to have a remarkably similar ability to lengthen the lives of melanoma patients, without the severe side effects of the new drug?

What if the other substance had no significant side effects at all? What if, instead of causing severe and sometimes fatal side effects, that other substance actually helped prevent and reduce serious side effects caused by chemotherapy and radiotherapy?

In fact, there is just such a treatment available. It is known as fermented wheat germ extract (FWGE) and by its trade name Avemar. It has been approved as a medical nutriment for cancer patients in Europe for years and is available in the US as a

dietary supplement. It has been compared to dacarbazine (DTIC), standard melanoma therapy, in a clinical trial with longer follow-up than the ipilimumab trial. And with better results.

In August 2008, data were published in the research journal *Cancer Biotherapy and Radiopharmaceuticals* from seven years' follow-up on a trial at the N. N. Blokhin Cancer Center in Moscow, Russia, involving 52 patients who had taken or not taken Avemar while taking dacarbazine for the year following surgical removal of their stage III melanoma tumors. (2)

Patients who got only dacarbazine survived 44.7 months. Those who got Avemar along with their dacarbazine survived 66.2 months. This is an improvement in overall survival time of over 48%.

In the Russian study, just as it has in other studies, Avemar reduced side effects of the chemotherapy. Among those taking only dacarbazine, 11 % experienced severe (grade 3 or grade 4) side effects that required hospitalization or invasive intervention. None of the Avemar patients had grade 3 or 4 side effects.

Since it is difficult to compare length of survival between the recent ipilimumab study and the Avemar melanoma study, because the ipilimumab study tested mostly stage 4 melanoma patients and the Avemar study tested mostly stage 3 melanoma patients, it is most instructive to look at the percentage improvement in overall survival from adding either treatment to the regimen. Ipilimumab and Avemar both produced very similar improvements in OS (56% vs. 48%, respectively), but the side effects from these two therapies are not comparable, nor is the QOL during treatment, with Avemar having a huge advantage.

Avemar Ameliorates Conventional Treatment Side Effects

The improvement of survival and the amelioration of chemotherapy side effects by Avemar seen in the Russian melanoma study is typical of Avemar's effects when used in treating other cancers, including in combination with chemotherapy or radiotherapy.

Among 170 colorectal cancer patients in a 2003 study published in the British journal of Cancer, Avemar improved overall survival and reduced metastasis and recurrences after surgery, chemotherapy, and radiotherapy. (3)

Taking Avemar for six months during and after those conventional treatments resulted in a 61.8% reduction in the death rate among those patients, compared with those who received only the conventional treatment. Those taking Avemar experienced lower rates of recurrences and metastases as well, even though most patients in the Avemar group came into the study with more advanced disease, had more radiation earlier, and had been diagnosed longer. Side effects of Avemar, as in other Avemar trials., were rare, mild, and transient, with no serious adverse events occurring.

In a 2004 study published in the journal of Pediatric Hematology and Oncology, childhood cancer patients taking Avemar during and after conventional therapies had a 42.8% reduction in the low white blood cell counts and high fever known as febrile neutropenia, which can be a life-threatening consequence of chemotherapy and radiation. (4) This and similar results with Avemar in other cancers are consistent with animal studies showing that Avemar helps the immune system recover a full white blood cell count after chemotherapy and radiation faster than would otherwise happen. This study also demonstrated the

safety of Avemar for children.

### Why Avemar Works in Many Different Kinds of Cancer

Extensive studies in cells and animals have shown how Avemar works. Perhaps its most important action is to restrict cancer cells' use of glucose. (5) Cancer cells use up to 50 times more glucose than normal cells, a phenomenon known as the Warburg effect. (6) They use those enormous amounts of glucose to make ribose, the backbone sugar of DNA, much faster than normal cells can. To do this, they must use a different series of biochemical reactions ("pathway") than normal cells. Avemar makes this very difficult for cancer cells to do, because it inhibits the activity of the key enzyme in that pathway, transketolase (TK). (7) With the TK pathway blocked, cancer cells cannot use large amounts of glucose to make DNA fast enough to support the proliferation that makes them so dangerous.(8-10)

In experiments in the US and abroad, scientists have learned that Avemar has these additional effects. It:

- \* lowers the levels of a DNA repair enzyme known as poly (ADP-ribose) polymerase (PARP)." With this effect, cancer cells are forced to self-destruct, preventing them from proliferating and producing a synergistic cancer-cell killing effect when given with chemotherapy, which also works to damage cancer cells' DNA;

- \* reduces the number of molecules on cancer cells that identify them as originating within the body (MHC-1 molecules). (12) With cancer cells stripped of that protection, the immune system, which recognizes the cancer cells as abnormal, no longer gives

them the pass given to cells originating in the body. The cancer cells are attacked by the immune system's natural killer (NK) cells and destroyed;

\* increases levels of molecules called intercellular adhesion molecule-1 (ICAM-1) on the blood vessels of cancer tumors. (13) The increase helps immune system cells pass through the walls of the blood vessels supplying the tumor blood flow, moving directly into the tumor to attack its cancer cells;

increases the activity of the primary anticancer cytokine, tumor necrosis factor alpha (TNF-a), and produces a synergistic effect in interaction with other anticancer cytokines. (14) Cytokines are substances produced by cells to act directly on other cells. TNF-a helps force cancer cells into the programmed death known as apoptosis and inhibits tumorigenesis, the process through which new tumors are formed;

\* inhibits the activity of ribonucleotide reductase (RR), a key enzyme that cells must have to make new DNA so that each cancer cell can divide to make two more like it. (15) With DNA production slowed, increases in cancer cell growth and replication are inhibited.

#### Antimetastatic and Immune-Boosting Effects Are Key to Survival

Because the biochemical changes listed above have consistently been shown in both animal and human studies to be directly linked to reducing cancer's ability to metastasize and to improving the immune system's ability to fight cancer, scientists count them as among the most likely main causes of improved survival seen in cancer patients when Avemar is used alone or, more often, as an adjuvant in addition to standard-of-care therapies such as chemotherapy, radiotherapy, or the

combination of the two. (16-23)

Extending Life: How Long, Exactly, and At What Cost in Quality of Life?

Any improvement in advanced melanoma survival, no matter how small, is certainly an achievement. But ipilimumab had severe side effects requiring hospitalization or invasive intervention in over one-quarter of patients treated with it. And it increased median survival only by 3-plus months. On the other hand, Avemar added to dacarbazine improved survival very markedly, with no severe side effects.

If actually improving overall survival substantially without significant side effects means that a drug should be considered as the new standard of care for first-line therapy, then there is no need to wait for further results. Avemar has already demonstrated very significant improvement in survival over chemotherapy alone and has a safety profile unmatched by conventional therapies. For those reasons, doctors--both naturopathic physicians and MDs--should take full advantage of this compound to give their patients with advanced melanoma the best possible outcome.

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