Complete Remission of Widely Metastatic Melanoma: A Case Report

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Melanoma has the potential to metastasize to any organ in the body. Patients with metastatic melanoma usually have a median survival of 6-9 months. A complete response was achieved when low dose IL-2 and GM-CSF were combined with high doses of intravenous vitamin C and glutathione, low doses of Temodar administered on a metronomic schedule, with magnolia extract. The clinical, radiological and histopathological features are discussed.

Melanoma has the potential to metastasize to any organ in the body. Patients with metastatic melanoma usually have a median survival of 6-9 months. We report a complete remission in an 80-year-old patient with malignant melanoma. The patient presented with pulmonary metastases and a history of multiple resections for local recurrence and in-transit metastasis. The following case seems worthy of a report because of a CR (complete response) when low dose IL-2 and GM-CSF were combined with high doses of Intravenous vitamin C and glutathione, low doses of Temodar administered on a metronomic schedule, with magnolia extract. The clinical, radiological and histopathological features are discussed.

Case Presentation
An 80-year old female with a past medical history of stage IV melanoma metastatic from a left foot primary with multiple prior resections of in-transit metastasis and right lung metastasis presented to the clinic on Dec 2011. She complained of extreme weakness, pruritus, rashes and left heel pain. On physical exam, the patient appeared toxic and was febrile. There was a 5x7cm, multilobulated, exophytic tumor with necrosis overlying the skin of the left anterior tibial region. A number of smaller cutaneous metastases were present proximally (Figure 1).

She had inguinal lymphadenopathy and 4+ edema of the left lower extremity. The tumor was inflamed with exudative weeping along with erythema and swelling in the surrounding area.

The patient’s relevant medical history dates from 2006 when she noted a lump in her left leg near the heel. She initially deferred evaluation of this, but eventually presented to a dermatologist where on October 2006, she had a biopsy of the lesion that showed invasive melanoma. Subsequently, she underwent a surgical consultation and later a wider excision with a sentinel node biopsy. The pathology report from the heel specimen described residual malignant invasive melanoma in situ and invasive to a Breslow depth of 2.4 mm of thickness, Clark level IV. Surgical margins were clear, and the tumor was noted to be present throughout the cicatrix. The sentinel node biopsies from the left inguinal area were negative for metastatic disease.

The patient had no evidence of disease over the next 2 years. By November 2008, she underwent an FNA biopsy of a left heel nodule near her initial resection site that confirmed metastatic melanoma. On December 2008, she underwent a left heel excision of a recurrent melanoma lesion. The patient 6 months later developed in-transit metastases, which led to multiple small subcutaneous nodules along the left anterior shin for which she had a biopsy that also confirmed metastatic malignant melanoma. In February 2010, the patient had another large metastatic lesion in her left leg. She underwent a biopsy and debulking of a metastatic melanoma in the superficial dermis with clear margins. She had a CT scan of the chest, abdomen and pelvis in September 2010 that revealed a 7x9 mm nodule at the right lung base consistent with new metastasis (Figure 2).

MRI of the left calf showed several new subcutaneous tumor deposits consistent with in-transit metastasis (Figure 3).

After refusing ipilimumab because of potential side effects, the patient presented at our integrative clinic to discuss treatment options for the progression of her disease. She was initially started on antibiotics (Ceftriaxone and Levofloxacin for severe left lower extremity cellulitis). A week later, leukine (250 mcg SQ twice weekly), vitamin C (50 grams IV weekly), proleukin (1million units SQ twice weekly), temozolamide (20 mg 5 days per week), actinretin (25mg orally three times per week) and Magnolia extract 200 mg (containing 90% honokiol and magnolol) daily by mouth, were added to her treatment regimen. The patient slowly improved over a few weeks as her cellulitis resolved. The vitamin C was given weekly for one year and continued every other week since September 2010. Glutathione 3000 mg. was given IV weekly for one year and continued every other week since September 2010. The leukine and proleukin were continued twice weekly since September 2010. After 3 months of treatment, the patient underwent PET-CT of the body and extremities in April 2012 that demonstrated significant resolution of previous metastatic lung lesion (Figure 4) and complete resolution of the subcutaneous and superficial lesions in her left leg (Figure 5).

Follow up PET-CT on October 2012 revealed no evidence of metastatic disease. There has been complete regression of the metastatic melanoma lesions in the
stage IV disease, the sites of metastasis and level of lactate dehydrogenase are the most important predictors of survival. Patients with distant skin or subcutaneous sites or distant lymph nodes have a 1-year survival rate of 59%. Patients with lung metastasis have a 10-year survival rate of less than 47%, whereas patients with metastasis to other visceral sites like the brain have a 10-year survival rate of < 30%. Cutaneous melanoma metastasizes more commonly to the lungs. A single focus of pulmonary metastasis is associated with a better survival than presence of multiple foci. Treatment of melanoma in its early stages is predominantly surgical and consists of excision of primary tumor with a 1-2 cm margin and radical lymphadenectomy if the sentinel lymph nodes harbor metastasis. Ipilimumab is a biologic response modifier which blocks cytotoxic T-lymphocyte antigen 4 has an overall response rate of 11% and improved median overall survival from 6.4 months to 10.1 months for patients with metastatic melanoma. Patients with metastatic disease with BRAF V600E mutation have an average progression free response (PFS) of 6.7 months, compared to 2.9 months in controls and a 50% response rate utilizing BRAF mutation specific inhibitors such as vemurafenib and dabrafenib.

Regarding its role in cancer treatment, vitamin C has been debated for many years. Emerging evidence indicates that ascorbic acid in cancer treatment deserves re-examination. Cameron and Pauling reported in 1976 and 1978 that high dose vitamin C (typically 10gms/day by IV in concentrations approaching Mm range) As established by seminal studies by Chen et al, vitamin C in concentrations higher than 1Mm can cause build up of hydrogen peroxide (H2O2) which is preferentially toxic towards tumor cells. Though the mystery of cytotoxicity to cancer cells remain unsolved, possibilities include stimulatory effects on apoptotic pathways, accelerated pro oxidant damage such as free radicals and peroxides. It is also involved in the modulation of immune response and detoxification of xenobiotics. In healthy living cells and tissues, more than 90% of total glutathione is in the reduced state (GSH) and less than 10% exists in disulfide form (GSSG). An increase in GSSG

Glutathione is an abundant natural tripeptide found within almost all cells. It is an important antioxidant that prevents damage to important cellular component caused by reactive oxygen species such as free radicals and peroxides. It is also involved in the modulation of immune response and detoxification of xenobiotics. In healthy living cells and tissues, more than 90% of total glutathione is in the reduced state (GSH) and less than 10% exists in disulfide form (GSSG). An increase in GSSG

Discussion
Malignant melanoma (MM) is a fatal cutaneous neoplasm, arising from the pigment producing cells (melanocytes) of the epidermis. Of the seven most common cancers in the US, melanoma is the only one whose incidence is increasing. Between 2000 and 2009, incidence climbed 1.9 percent annually. Melanoma accounts for less than five percent of skin cancer cases, but the vast majority of skin cancer deaths. It is usually described as an irregular dark skin lesion that may have areas of varying color in sun-exposed areas or in unexposed areas. Early diagnosis is crucial, as metastatic or advanced disease is associated with poorer prognosis. The commonest site of presentation for men tends to be the trunk, and for women is the lower limb.

The most common cause of death in melanoma is widespread metastasis. Staging in melanoma is based on primary tumor thickness, ulceration, lymph node and distant metastasis. The American Joint Commission on Cancer (AJCC) TNM system is the most commonly used melanoma staging system. Stage I and II of this system are comprised of patients without regional or distant metastasis. Stage III patients have metastasis either in the regional lymph nodes or intra-lymphatic sites. Stage IV patients have visceral metastasis in distant sites. The thickness and ulceration of melanoma are important in criteria assessing survival in patients with localized disease (Stage I and Stage II). In patients with left lower leg (Figure 6). Currently, the patient’s clinical status remains excellent as she continues in complete remission.

Figure 2
Chest CT scan showing 7x9 mm. pulmonary nodule (shown by arrow) at right lung base suspicious for potential metastasis from primary melanoma in the left lower leg.

Figure 3
MRI combined with PET-CT of the extremities showing in-transit metastasis of melanoma in the left lower leg represented by hyper-metabolic yellow areas.
to GSH ratio is considered oxidative stress, which is implicated in cancer progression.\textsuperscript{18} The intracellular depletion of glutathione leading to cell death has been extensively researched for decades. GSH levels in human tissue normally range from 0.1mM, most concentrated in liver, spleen, kidney, lens, erythrocytes and leucocytes. Oxidative stressors that can deplete GSH include ultraviolet rays and other radiation, viral infections, environmental toxins, heavy metals, surgery, inflammation, burns, septic shock, and dietary deficiencies of GSH precursors.\textsuperscript{19,20} The immune system function is dependent upon the lymphoid cells having a delicately balanced, adequate level of glutathione. Certain functions such as orderly DNA synthesis are exquisitely sensitive to reactive oxygen species and therefore improved by high levels of antioxidant glutathione. Certain signaling pathways, in contrast, are enhanced by oxidative conditions and favored by low glutathione levels. IL-2 dependent functions including T-cell proliferation, cytotoxic T-cell activity, lymphokine activated killer cells and natural killer cells are particularly sensitive to glutathione depletion.\textsuperscript{21} It has been demonstrated that exogenous, extra cellular glutathione induces apoptosis in ovarian cancer cell lines by inducing expression of the PS3 and P21 tumor suppressor genes.\textsuperscript{24}

Honokiol and magnolol (isomer of Honokiol) have shown to inhibit skin tumor growth and invasion.\textsuperscript{25} The nuclear transcription factor nuclear factor (NF-Kb) is involved in the expression of several genes whose products are involved in tumorogenesis. These include antiapoptotic genes (survivin, TRAF, Bcl-2, bcl-x), cyclooxygenase (COX-2), matrix metalloproteinase (MMP-9), vascular endothelial growth factor (VEGF), and cell cycle regulatory genes (cyclin D1 and c-myc). Honokiol downregulates the expression of the abovementioned products and thus prevents proliferation and metastasis of cancer.\textsuperscript{26,27,28} It also potentiates apoptosis induced by TNF and chemotherapeutic agents.\textsuperscript{29}

In patients with advanced melanoma, treatment with temozolomide is associated with greater improvements in overall survival.\textsuperscript{30} Temozolomide is a novel oral alkylating agent, which appears to exert its therapeutic benefit through DNA methylation and therefore triggering the death of neoplastic cells. Its acceptable safety profile and predictable pharmacokinetics make temozolomide an excellent candidate for inclusion in combination therapies for advanced metastatic melanoma. Temozolomide, which is 100% orally bioavailable, allows for outpatient treatment. This is particularly desirable for patients with advanced melanoma, a group with a short life expectancy and a low rate of response to treatment. In clinical studies, temozolomide was well tolerated and demonstrated rapidly reversible, mild to moderate myelosuppression.\textsuperscript{31}

However given this patient’s concurrent infection and advanced age, conventional dosing of temozolomide was contraindicated. Metronomic dose chemotherapy has been found to be well tolerated,\textsuperscript{32} and have both pro-apoptotic\textsuperscript{33} and anti-angiogenic effects\textsuperscript{34} in multiple tumor types.

Based on several clinical studies, vitamin A has been observed to interfere with the carcinogenic process in different ways. Inhibition of malignant melanoma cell proliferation through Fas death receptor pathway mediated cell apoptosis,\textsuperscript{35} inhibition of proliferation of melanoma cells through cell cycle arrest\textsuperscript{36} appear to be some of the proposed mechanisms of vitamin A against malignant melanoma.

Natural plant extracts, such as polyphenolic antioxidants found in green tea and grape seed, have been shown to inhibit tumor angiogenesis and tumor growth through a number of mechanisms.\textsuperscript{37} Epigallocatechin-3-gallate (EGCG), the major catechin (flavonol) in green tea was found to result in a dose-dependent decrease in the viability and growth of melanoma cells.\textsuperscript{38} Interestingly, at similar EGCG concentrations, the normal melanocytes were not affected. EGCG treatment of the melanoma cell lines resulted in decreased cell proliferation and induction of apoptosis via downmodulation of anti-apoptotic protein Bcl2, upregulation of proapoptotic Bax and activation of caspases.\textsuperscript{39} EGCG also causes significant induction of cell cycle arrest via modulations in the cki-cyclin-cdk network. Thus, EGCG, alone or in conjunction with current therapies, could be useful for the management of melanoma. Sinecatechin (trade name Veregen) is an ointment of catechins (55% epigallocatechin gallate) extracted from green tea and other components. It was the first botanical prescription drug approved by the US Food and Drug Administration, for treatment of genital warts caused by the Human Papilloma Virus.\textsuperscript{40}

**Conclusion**

Late presentation of metastatic melanoma is common, and should be remembered in patients with a distant history of melanoma. Follow-up is necessary in order to diagnose potential dissemination or secondary sites of the disease. In stage-IV melanoma, Temodar, IL-2 therapy combined with retinoic acid, vitamin C, topical sinecatechin, magnolol, glutathione and sargramostim demonstrates a promising alternative/complementary regimen to standard regimens for treatment of metastatic melanoma. Temodar was added on metronomic schedule for its broadspectrum antitumor activity via promoting apoptosis and inhibiting angiogenesis with limited side effects. Magnolol, vitamin C, vitamin A, and topical sinecatechin were included because of their proapoptotic properties.
against melanoma cells. IL-2 even in low doses regulates cellular immune response. Glutathione has immune-stimulating and pro-apoptotic effects. Sargramostim stimulates the bone marrow to produce natural killer cells. This patient has remained in complete remission for 25 months and is tolerating the regimen without side effects. Further investigation of this combination of low dose immune modulating agents, chemotherapy and bioactive nutrients is warranted.

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References for this article may be found at http://www.cancerstrategiesjournal.com/ReferencesVolume2Issue2.pdf

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