

Successfull pain management with radiotherapy and ozone therapy in a case of metastatic, chemotherapy resistant sino-nasal mucosal malignant melanoma

Abstract

Background: Nasal mucosal and paranasal sinus melanomas are rare tumours of head and neck region. Regional recurrence and distant metastasis are very high despite with surgery, chemotherapy, immunotherapy and radiotherapy in these tumours. Coping with pain can sometimes be quite difficult in metastatic disease.

Case: In our sino-nasal mucosal melanoma (SNMM) case, disease was progressed following chemotherapy (CT) and head and neck radiotherapy (RT), despite a full response was obtained in the primary tumour. The patients have severe pain that exacerbated even with using high dose opioids due to metastases developing in the adrenal and pancreatic regions. Ozone therapy was applied up to 2cm from the level of the umbilicus at deep as 2cm only one dose with local RT of adrenal and pancreatic regions.

A complete palliation was obtained in pain and the opioids were interrupted. There was no pain in the last 3 months until death without any pain treatment.

Discussion: In our case, a full pain control was achieved with ozone therapy initiated following the progression after CT and head and neck RT.

Keywords: sinusal/sinonasal/paranasal malignant melanoma, radiotherapy, temozolomide, ozone therapy

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Introduction

The most common location of malignant melanoma (MM) is the head and neck region (25-30%). SNMM is a very rare and an aggressive progressive type of MM.¹⁻³ Mucosal MM usually presents at a more advanced stage and is therefore associated with a higher mortality rate than cutaneous melanoma because of its location and rich vascularization.^{4,5} The best outcomes are achieved with postoperative radiotherapy in operable cases. Survival rates have been increased with the addition of radiotherapy and immunotherapy to surgery.⁹⁻¹² Cisplatin, dacarbazine and vindesine combination is one of the best chemotherapy regimens in patients with metastatic disease⁸ In a meta-analysis, nasal mucosal melanoma had a 31% 5-year survival rate, whereas sinus melanoma patients had a 0% 5-year survival.¹³ Distant spread in general is associated with rapid clinical deterioration and a short survival time.²⁵

If the cancer-related pain is not treated, it disrupts and decreases sleeping, appetite, treatment tolerance, quality of life and performance status of patients.¹³ Opioids usually using for severe pain despite their side effects. Cancer-related pain may be many different reasons than normal pain. The cause of cancer pain can be inflammatory, neuropathic or pain mediators.¹⁴

Palliative radiotherapy is most commonly used for pain in metastatic cancer.¹⁵ One of the factors reducing the beneficial effects of radiotherapy in rapidly growing tumors were become oxygen-starved because of a lack of sufficient vascular support. The hypoxia is an important factor in radio resistance, differentiation of tumor cells metastasis and neovascularization.^{16,17} Medical ozone (5% Ozone and 95%oxygen mixture) (OO)therapy which increases oxygenation on tissues can be used for treatment of inflammation, ischemic illnesses and pain palliation.¹⁸⁻²⁰

OO therapy can increase the sensitivity and decrease the side effects of radiotherapy causing increase in the red blood cell glycol sis rate, and the stimulation of 2,3-diphosphoglycerate.²¹ The cytotoxic and radiosensitive effects of OO determined to lung, breast, uterine, and ovarian cancer cells by increasing the production of interferon, tumor necrosis factor, and interleukin-2.²²⁻²⁵

The World Health Organization (WHO) updated pain management guidelines.²⁶ According to these guidelines, obtained a three-stage pain management for pain of cancer. If resistance of pain available even these analgesic treatments, interventional treatment planning of pain may be a good option.²⁷ Interventional pain management can be applied to such as joint injections, radiofrequency ablation,

nerve blocks, OO injections, and cement augmentation techniques to treatment of pain which resistant to conventional management.²⁷ OO can also reduce pain by reducing inflammation with anti-bacterial, anti-fungal and anti-viral effects.^{28,29} OO known to have a important role along with other standard treatments as is determined by other studies.^{30,31}

Case report

Our case is a 54-year-old male patient who diagnosed as SNNM (Figure 1). His disease was progressed following chemotherapy (CT) and radiotherapy (RT), despite a full response was obtained in the primary tumour with RT. ECOG (Eastern Cooperative Oncology Group) performance scoring was 4, Visual Analog Scoring (VAS) was 100%. His FDG PET CT (Positron emission tomography with fluorine 18 (18F) fluorodeoxyglucose and computed tomography) images showed big tumour in the pancreas and left adrenal gland, the biggest one being 11cm.

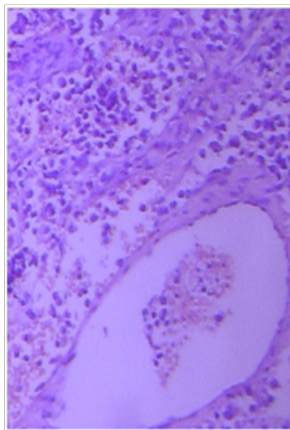


Figure 1 Histopathological image of SNNM (HE staining 40x10).

The patient have severe pain that exacerbated even with using high dose opioids due to metastases developing in the adrenal and pancreatic regions. The palliative RT was planned with CT simulation, fraction of 250cGy with dynamic IMRT once a day and five days a week to adrenal and pancreatic regions. But After 4 fraction of RT, the pain became more severe even using opioid.

OO therapy was applied up to 2cm from the level of the umbilicus at deep as 2cm 20mcg/ml, 2ml/dose, only one dose with RT.

A complete palliation was obtained in pain and the opioids were interrupted. A new VAS was 0%. The patient's performance improved from ECOG 4 to ECOG 3 after OO with RT. There was no pain in the last 3months until death without any pain treatment.

Discussion

In early stage mucosal malignant melanoma, generally, a 50-75% onset response was reported to be achieved with radiotherapy.^{32,33} In metastatic melanoma, 21% response was achieved with temozolomide treatment.³⁴ In recent years, favourable results have been obtained with Src inhibitors. The Src inhibitors dasatinib and bosutinib can be used alone or with chemotherapy.³⁵ Vemurafenib and ipilimumab are promising drugs that are recently approved for melanoma treatment.^{36,37} One of the most important reasons for chemo resistance in nasal mucosal malignant melanomas is the inadequacy of apoptosis; and one of the most important reasons for this is lack of

oxygenation in the tumour.³⁸ A good local control may be obtained with radiotherapy, but survival advantage has not been demonstrated with radiotherapy alone.³⁹ In one study, Ozone was found to be more effective in tissues have intensive c-kit levels.⁴⁰⁻⁴² Interestingly, over expression of c-KIT, a receptor tyrosine kinase, was reported in 39% to 88% of mucosal melanomas.^{43,44} This mutation was associated also with sensitivity to imatinib in vitro. The c-KIT is a key regulator of mucosal melanoma and proliferation of melanocytes.⁴⁵ It has been shown to activate the intracellular signaling pathways related to tumour progression.⁴⁶ Marked tumour regression was observed in metastatic mucosal melanoma with single-agent imatinib.⁴⁷ These evidences may be indicates imatinib and OO probably show additive effects on melanoma for additive to CT or pain treatment in future.

OO therapy which increases oxygenation on the issues can be used for treatment of inflammation, ischemic illnesses and pain palliation.¹⁸⁻²⁰ A faster and more effects can be obtained by injecting of OO into a painful spot. This is also called indirect approach or chemical acupuncture.⁴⁸⁻⁴⁹

In our metastaticsinonasal mucosal melanoma case, disease was progressed and metastasized to pancreas and adrenal gland after CT and head and neck RT. Injection of OO treatment was applied for resistant pain despite opioids due to a big metastatic mass. It has become addicted to bedding due to lose of appetite, cachexia and severe pain complaints. The patient's performance improved from ECOG 4 to ECOG 3 after RT and OO. Although he was treated with only 1 session and 3ml injections, the pain was completely improved and opioids interrupted.

OO can help to reduce cancer related pain and other side effects and improves to overall quality of life causing decreasing of pain and side effects. There is a great need for multicenter studies for OO treatment and pain management of malign melanoma and other cancers with severe pain.

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Conflict of interest

The author declares no conflict of interest.

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