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Case Report-A learning from clinical experiential history

Cyaplex F 를 적용한 외래환자 증례보고: Imatinib 의 부작용 완화

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An outpatient case study of Cyaplex F: mitigated adverse effects associated with Imatinib

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ABSTRACT

Objective: A case of reducing adverse effects associated with imatinib using Cyaplex F.

Methods: The 52-year-old female with past medical history of stage 1 triple-positive breast cancer 10 years ago, and current metastatic melanoma has been complaining adverse effects after imatinib was started.

Results: After OCNT was initiated, the patient's headache and muscle pain have been much tolerable and her AST/CPK levels were returned close to her baseline.

Conclusion: OCNT may reduce side effects caused by Imatinib and help patient to stay with the current chemotherapy regimen.

Keywords Ortho-Cellular Nutrition Therapy (OCNT), breast cancer, melanoma, headache, muscle pain, AST, CPK

Introduction

Breast cancer can be a fatal disease in which abnormal cell tissue grows in the breast or spreads to other organs. Although breast cancer is the most studied of all cancers, it is not clear that environmental and genetic factors are the main cause, with no established theory regarding the cause of breast cancer. However, several research results show a high correlation between several factors, and among them, the female hormone estrogen is believed to play an important role in the carcinogenesis process.[1] Breast cells proliferate and differentiate under the stimulation of estrogen. Thus, it is believed that an individual's risk of developing breast cancer is ultimately determined by the total

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period of exposure to estrogen during one's lifetime. In other words, the longer the exposure period to estrogen, the greater the incidence of breast cancer.[2] Various standards for the classification of breast cancer depend on the pattern of occurrence, which divides breast cancer into several categories. Among them, hormones recognized by receptors present in cells may cause mutations. Breast cancer cells may have multiple such receptors, but in some cases, they may have no receptors. Among these receptors, three receptors are expected to be most associated with breast cancer: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). If all three receptors are present in breast cancer cells, it is classified as triple-positive breast cancer.

Melanoma is a skin cancer that begins in melanocytes, typically caused by DNA damage due to exposure to ultraviolet rays from the sun. However, it can also occur in areas of the skin that are rarely exposed to sunlight, and genetic factors also contribute to some extent, so if a family member has suffered from melanoma, the risk of developing it is higher. People with mutations in the MC1R gene often have red hair, and the likelihood of developing melanoma is two to four times higher in these people than in the general population. If tumor cells are located only in the skin epidermis and are in the radial growth phase with a thickness of less than 1 mm, extensive surgical resection, including the normal skin border, can be performed to remove all malignant cells while minimizing the risk of local recurrence.[3] However, if tumor cells enter the vertical growth phase, they spread throughout the body through blood vessels and lymphocytes, so tumor development must be prevented through immunotherapy, radiation therapy, and chemotherapy.[4]

The patient was diagnosed with stage 1 triple-positive breast cancer ten years ago, underwent a partial mastectomy, and was treated with six cycles of TCH (Taxotere/Carboplatin/Herceptin) and radiation therapy. Afterward, due to the development of malignant melanoma, surgical resection was done and she was treated with a series of intravenous immunotherapy with nivolumab/ipilimumab, which was unexpectedly discontinued due to grade 4 CNS toxicity. Later, she was prescribed oral imatinib 400 mg/day by oncology to prevent the recurrence of a malignant tumor. However, the patient experienced abrupt adverse effects such as persistent severe headaches, severe muscle pain, and increased aspartate transaminase (AST) and creatine phosphokinase (CPK) blood levels. At this point, she was introduced to OCNT and we would like to submit her progress report.

Case Details

1. Subject

One case of a melanoma patient was studied.

1) Name: Jane Doe (F/52 years old)

2) Diagnosis: malignant melanoma

3) Date of onset: 2013

4) Treatment period: approximately eight years

5) Major complaints w/ Imatinib: Headache (symptom scale score: 7-8 out of 10), muscle pain (very severe pain, interfering with daily life)

6) Past history: breast cancer

7) Social history: occasional alcohol / tabacco user

8) Family history of cancer: None

9) Current medication: imatinib 300 mg daily

2. Methods

Cyaplex F powder: one pouch three times a day on empty stomach

Results

The patient in this case study complained of various adverse effects after taking imatinib 400 mg/day prescribed by an affiliated facility of MD Anderson Cancer Center, Texas. Main complaints were headaches and muscle pain, and abnormal blood lab results of AST, increased to 69 U/L (normal level 14-36 U/L), and of CPK level increased to 394 U/L (normal level 30-135 U/L). Due to these adverse effects, imatinib was on hold for seven days. Afterward, the patient's AST/CPK levels returned to normal, and headaches was gone. However, when the patient restarted imatinib at a lower dose of 300 mg/day, the AST/CPK levels elevated again, and headaches came back. In this situation, other alternative intervention was needed to prevent the recurrence of malignant tumor while managing adverse effects. Therefore, OCNT (Cyaplex F) was added to imatinib 300 mg/day, and blood lab was repeated every 3-4 weeks. Surprisingly, her headache completely disappeared within two days with OCNT, and her muscle pain also seemed to be reduced. Four weeks later, another test showed that her AST/CPK levels were significantly improved (Figures 1 and 2). In addition, while taking imatinib, the patient's WBC level tended to decreased below normal range. However, the level of WBC steadily increased after taking Cyaplex F together (Figure 3).

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Imatinib (mg)	400	400	HOLD	300	+ CYP	+CYP
AST (14-36U/L)	69	42	29	79	42	37

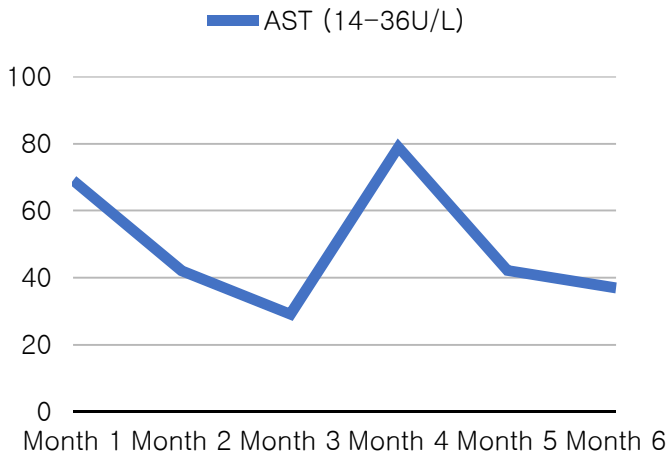
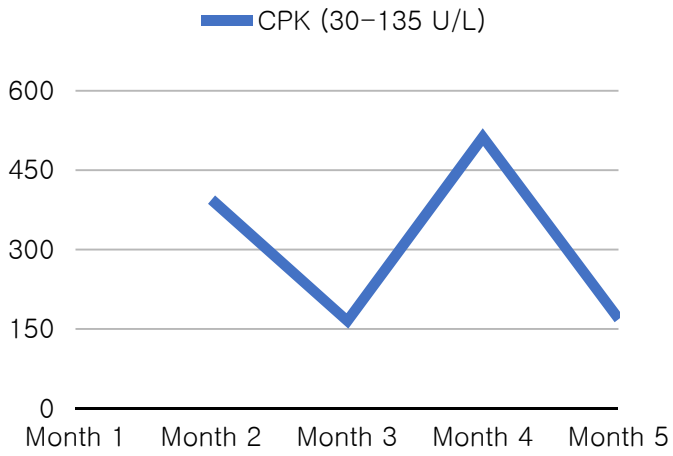


Figure 1. Changes in patient's AST levels before/after OCNT. As shown in Fig. 1, after the initial dose of imatinib, the AST level was 69 U/L, which was outside the normal range, so imatinib was on hold for a while (month 3). Afterward, imatinib was restarted, and the AST level increased rapidly above the normal range. However, when taking imatinib in combination with Cyaplex F, AST level finally started to go back to her baseline of 37 U/L.

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Imatinib (mg)	400	400	HOLD	300	+ CYP	+CYP
CPK (30-135 U/L)		394	165	512	168	

Figure 2. Changes in the patient's CPK levels before/after OCNT. Two months after taking imatinib, the



patient's CPK level was high at 394 U/L, so imatinib was temporarily discontinued. Afterward, the CPK levels tended to increase quickly when imatinib was retaken. When imatinib was combined with Cyaplex F from Month 5, the CPK level decreased to 168 U/L.

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Imatinib (mg)	400	400	HOLD	300	+ CYP	+CYP
WBC (3.2-11 K/CUMM)		2.6	5.0	2.7	3.2	3.8

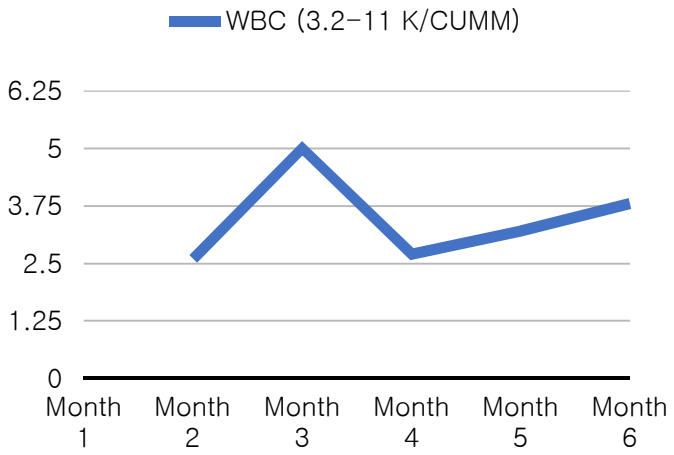


Figure 3. Change in the patient's WBC count before/after OCNT. When taking imatinib, the number of WBCs tends to decrease. However, when taken together with Cyaplex F, the WBC level gradually increases as shown in Fig. 3.

Discussion

Imatinib, an antineoplastic agent, acts as an inhibitor of Bcr-Abl tyrosine kinase to inhibit the proliferation of tumor cells and is also used in the treatment of chronic myelogenous leukemia (CML), gastrointestinal stromal tumor (GIST), dermatofibrosarcoma protuberans (DFSP), myelodysplastic syndrome/myeloproliferative disease (MDS/MPD), aggressive systemic mastocytosis (ASM).[5] Imatinib specifically inhibits various tyrosine kinases, including CSF1R, ABL, c-KIT, FLT3, and PDGFR-β.[6,7] Unlike existing anticancer drugs, it is a drug that has excellently suppressed adverse effects, so it is known that there are no major adverse effects. However, skin rash, vomiting, headache, joint pain, and muscle pain may occur in a small pool of patients. In severe cases, fluid retention, gastrointestinal bleeding, bone marrow suppression, liver problems, and heart failure are also reported.[5]

The patient in this case study was previously diagnosed with triple-positive breast cancer and malignant melanoma and was prescribed imatinib to prevent the recurrence of the tumor. However, after taking the medication, she complained of headache and muscle pain and showed abnormalities in AST and CPK levels. The exact cause of muscle pain is unknown, but it is believed to be due to abnormal pain perception. People with fibromyalgia may have reduced serotonin metabolism in the central nervous system and may have abnormalities such as decreased growth hormone and adrenocortical hormone and dysfunction of the autonomic nervous system.

Quercetin contained in Cyaplex F has been known through in vitro experiments to act as an inhibitor of cytochrome P450 enzymes, CYP3A4, CYP2C19, and CYP2D6.[8] In particular, CYP2D6 is reportedly involved in the metabolism of amitriptyline, which is an antidepressant and is used to treat muscle pain.[9] In addition, this enzyme metabolizes several endogenous substances, such as hydroxy tryptamine and neuro steroids. CYP2D6 is involved in synthesizing m-tyramine and p-tyramine into dopamine in the brain and liver.[10,11] Therefore, consuming quercetin can help reduce muscle pain by improving the function of the central and autonomic nervous systems. An increase in AST and CPK levels indicates damage to muscles, liver, and heart, and the patient showed an increase of up to 3 to 4 times compared to standard levels after taking imatinib. It has been reported that fucoidan contained in Cyaplex F improves indicators of liver damage, such as cirrhosis, when patients with liver disease take it consistently, and anthocyanin has been found to protect heart cells through antioxidant activity and help with various heart diseases.[12,13] Therefore, after taking imatinib, the patient suffered damage to the liver and heart muscle, and Cyaplex F is thought to help relieve symptoms by protecting cells from such damage. Aronia extract contained in Cyaplex F shows antioxidant properties in plasma and platelets in ordinary people and breast cancer patients. Therefore, when administered to patients undergoing breast cancer treatment or chemotherapy after surgery, it seems to significantly reduce oxidative/nitrogen stress in the platelets of breast cancer patients.[14] In addition, anthocyanin, the most potent antioxidant among plant flavonoids, has been reported to have antioxidant and anti-inflammatory functions and has been found to be involved in the growth inhibition response of tumor cells through in vitro experiments.[15,16]

The patient's treatment is continually being monitored by her Oncology and affiliated Integrated Medicine Department. She takes ibuprofen due to occasional mild headaches, which is not considered an adverse effect of imatinib because the patient had occasionally experienced headaches even before the onset of breast cancer. This case study discusses a single case and may not be universally applicable to other melanoma patients, with limitations in interpreting the test results.

Nonetheless, adding Cyaflex F to her anti-cancer drug regimen improved her qualify of life and helped her to continue her cancer treatment. This case study is reported with the patient's consent.

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