Rhinology, 35, 19–21, 1997

Chemohormonal therapy for malignant melanomas of the nasal and paranasal mucosa*

Wataru Seo, Hiroshi Ogasawara, Masafumi Sakagami

Department of Otorhinolaryngology, Hyogo College of Medicine, Nishinomiya, Japan

SUMMARY

We present three cases of primary malignant melanoma of the nasal or paranasal mucosa that were successfully treated by chemohormonal therapy using tamoxifen (TAM), an anti-estrogen agent. All of the patients showed good responses. TAM is widely known to be an anti-estrogen chemotherapeutic agent in the treatment of breast cancer and is thought to exert its anti-neoplastic effect in breast cancer tissues by competing with estrogen for estrogen receptors. The mechanism of the effect of TAM in malignant melanoma is not yet known. Although its anti-neoplastic mechanism requires further exploration, we believe that chemohormonal therapy may become important in multidisciplinary treatment of malignant melanoma of the nasal and paranasal mucosa.

Keywords: malignant melanoma, chemohormonal therapy, tamoxifen, estrogen receptor

INTRODUCTION

The prognosis of malignant melanoma is very poor, especially when it originates in the head-and-neck region in such structures as the nasal or paranasal sinus or oral mucosa. Although surgical therapy, radiotherapy, chemotherapy, immunotherapy, interferon therapy, and other therapies have been suggested for the treatment of this malignant disease, there is still no therapy established as definitely effective. We have used various types of therapies in our attempts to treat our patients with primary nasal or paranasal malignant melanoma, but with unsatisfactory results. However, we performed chemotherapy using the anti-estrogen agent tamoxifen (TAM) with satisfactory results in 3 patients. The regimen of chemohormonal therapy was a modification according to McClay et al. (1993a). We describe the clinical course in each patient treated with chemohormonal therapy including TAM.

PATIENTS AND METHODS

Case 1

A 55-year-old man who had had epistaxis of the left nose since January 1988 consulted us in July 1988. A tumorous lesion was found in the nasal cavity, and the biopsy sample was diagnosed as malignant melanoma of the nasal cavity. The patient underwent chemotherapy with dacarbazine (DTlC), vinblastine (VBL) as well as cisplatin (CDDP), lateral rhinotomy and interferon therapy, but the lesion could not be controlled. During the observation of the clinical course, blepharoptosis of the left eye and double vision suddenly developed in December 1992. The left eyelid drooped, the eye opened only narrowly, and all eye muscles were paralysed accompanied by double vision in all directions. By anterior rhinoscopy, both nasal cavities were found to be filled with haemorrhagic black tumour. No enlargement of lymph nodes or other change was observed. The tumour was resected immediately, but it recurred again rapidly. Since the patient became partially comatose, possibly due to compression of the brain by the tumour, chemohormonal therapy including tamoxifen (Nolvadex®) was started. The regimen of chemohormonal therapy was a modification of that described by McClay et al. (1993a), in that carmustine (BCNU) was replaced by ranimustine (MCNU; Table 1).

Table 1. Regimen of chemohormonal therapy in our patients.

dacarbazine (DTIC): 300 mg/day, 3 days
cisplatin (CDDP): 30 mg/day, 3 days
ranimustine (MCNU): 200 mg once, every 4 weeks
tamoxifen (TAM): 20 mg twice daily, every 8 weeks

During chemohormonal therapy, the tumour in the nasal cavities gradually shrank, and the patient's consciousness was gradually restored in about five days. After chemohormonal therapy for two months, no tumour lesion could be observed by endoscopy nor could any tumour cells be seen in biopsy material, and therefore we considered that a complete response (CR) was obtained. Also, the patient was free of the paralysis of the eye muscles. The patient was in remission for 20 months after

* Received for publication March 28, 1996; accepted October 16, 1996

discharge, but died due to adult respiratory distress syndrome (ARDS) associated with pneumonia. During autopsy the diagnosis of idiopathic ARDS was confirmed.

Case 2

A 59-year-old woman had been suffering from epistaxis in the right nose since January 1992 and was referred to our department in June of the same year. She had a history of hypertension, cerebral aneurysm, and hepatitis type C. Upon first examination, a dark-red haemorrhagic tumour extending from the middle to the common nasal meatus was found at anterior rhinoscopy. No lymph nodes were felt on palpation in the cervical region or any other part of the body. Computed tomography revealed a lesion originating from the right anterior ethmoidal region, and protruding into the nasal cavity (Figure 1a). During histopathological examination it was identified as a malignant melanoma. After hospitalization, she underwent two courses of chemotherapy consisting mainly of DTIC, followed by intermittent radiotherapy at high dose (60 Gy each). Since shrinkage of the tumour was incomplete, the treatment was replaced with chemohormonal therapy using TAM, starting in October 1992. The regimen was the same as that used in case No. 1 (vide supra). After the start of chemohormonal therapy, the tumour shrank macroscopically and disappeared in about 2 months. The epistaxis also disappeared. During treatment, a decrease in platelet count was observed temporarily, but the count recovered later. The CT scan after the chemohormonal therapy showed resolution of opacification in the maxillary sinus and the anterior ethmoidal region (Figure 1b). No tumour was observed macroscopically or histopathologically. For about 44 months thereafter, she has shown complete response, and she is presently under observation.

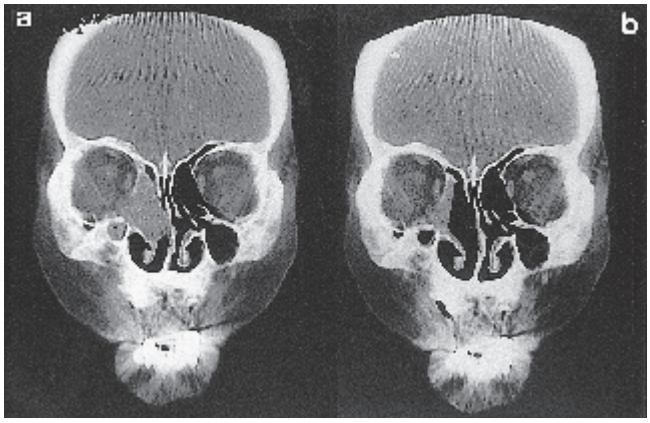

Figure 1. (A) Pretreatment: The CT scan discloses an occupying lesion originating from part of the right maxillary sinus, and protruding into the nasal cavity. (B) Post-treatment: The tumour in the nasal cavity has shrunken considerably.

Case 3

A 66-year-old woman had been suffering from nasal obstruction in the left nose since January 1993. A tumorous lesion extending from the inferior to the middle nasal meatus was diagnosed as malignant melanoma by biopsy (Figure 2). She immediately underwent surgical resection at another hospital, but in spite of the surgical treatment, the lesion rapidly recurred. She was referred to our department in August 1993. At first examination, by anterior rhinoscopy, the tumour was observed to occupy the inferior nasal meatus. No enlargement of lymph nodes or other changes were observed. After she was hospitalized, chemohormonal therapy was started. Thereafter, the tumour shrunk macroscopically and disappeared in about 4 months. During treatment, she showed no toxic side effects. She has been in remission for 30 months, and she is now under observation.

DISCUSSION

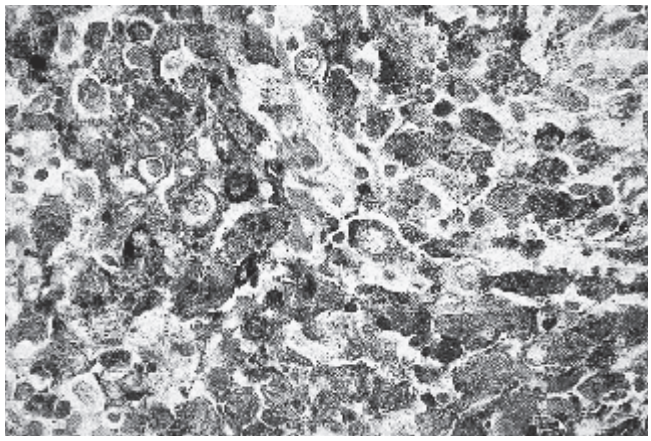

Figure 2. Fine melanin granules are present in the malignant cells located in the mucosa of the nasal cavity (haematoxylin and eosin, ×400).

The rarity of malignant melanoma of the nasal cavity and paranasal sinuses compromises any evaluation of management. These tumours are associated with a poor prognosis and unpredictable course (Lund, 1993). The fundamental treatment of a tumour is the control of primary lesions (Lee et al., 1994), but this is often impossible. The ideal therapy is complete surgical removal of the primary lesion in the early stage, before metastasis to the lymph nodes. However, total surgical excision is rarely possible anatomically in the head-and-neck region, and therefore several types of alternative treatments have been attempted. In addition, mucosal malignant melanomas appear to be more aggressive than cutaneous melanomas.

In spite of our attempts to apply various methods (such as surgery, chemo-, radio- and immunotherapy) in the treatment of malignant melanoma, we were unable to obtain any satisfactory results. However, we did obtain good results – consistent with the report of McClay et al. (1992) – by using chemohormonal therapy consisting of TAM, DTIC, CDDP and MCNU. McClay et al. (1992) administered chemohormonal therapy to patients with malignant melanoma and compared treatment results obtained with and without the use of TAM; good results were observed in patients receiving TAM in combination. They also observed an increase in the mean survival time. As side effects, they described general oligocythemia, mainly thrombocytopenia, together with inevitable nausea and vomiting. In our patients, a slight but transient thrombocytopenia was observed in addition to nausea and vomiting, but no problematic effects were detected.

TAM is probably more well known as a therapeutic agent for breast cancer. Its anti-neoplastic effect is thought to be due to anti-estrogen activity, which is based upon competitive binding

to estrogen receptors in the tumour. However, the mechanism of the action of TAM against malignant melanoma has not yet been clarified.

Nesbit et al. (1979) treated patients for progressive malignant melanoma with TAM alone, and found a response in approximately 30%; a particularly good response was found in patients with tumours in soft tissues. Since the mechanism of action was not clear, they speculated that the effect was due to an indirect rather than a direct action of the estrogen receptor. Later, Masiel et al. (1981) and Creagan et al. (1980) reported that single-agent TAM therapy was effective in treating malignant melanoma.

Mirimanoff et al. (1981) administered TAM to patients with recurrent malignant melanoma and secured complete response for a long period, suggesting the hormonal dependency of malignant melanoma. In addition, Fischer et al. (1976) confirmed the presence of estrogen receptor in about 46% of cases of malignant melanoma. However, others have reported that the presence of estrogen receptor is not always related to the efficacy of TAM on malignant melanoma (Papac et al., 1980; Fisher et al., 1981). In fact, no estrogen receptor has been detected in case No. 1 in the present study.

Regarding the efficacy of TAM, Del Prete et al. (1984) reported that combined use of TAM and CDDP was much more effective than TAM alone. McClay et al. (1992) asserted that the combined therapy was effective for malignant melanoma because of the sensitizing effect of TAM on CDDP activity. According to their recent paper (McClay et al., 1993b), mutual interactions of sensitizing activity between TAM and CDDP were observed not only in malignant melanoma but also in small cell carcinoma of the lung and ovarian cancer, and this combination therapy is effective. In another report (McClay et al., 1993a), they presented a case of malignant melanoma which had been resistant to CDDP therapy but showed good response after the addition of TAM.

The mechanism of this interaction is unclear at present. It has been tried to explain the interaction between TAM and CDDP in various fundamental studies. Hofmann et al. (1988) have demonstrated a marked decrease in cellular proliferation when TAM was added to CDDP in culture with Walker-rat carcinoma cells. When TAM, a protein-kinase-C inhibitor, was added to the system in various concentrations, the dose-effect curve for the inhibition of protein-kinase-C inhibitor closely resembled the dose-effect curves of the anti-proliferative activities. They hypothesized that TAM enhances the capacity of CDDP by interacting with the membrane fraction of protein kinase C, interfering with important signal transduction pathways required for cell growth. Mann et al. (1989) have suggested reported an alternative explanation, relating to cAMP levels.

Since chemohormonal therapy for malignant melanoma in the paranasal sinuses has not been reported, the present study is the first one to suggest a possible efficacy in this entity. It is necessary to clarify the mechanism of the effective action of chemohormonal therapy. In the future, chemohormonal therapy may play a very important role in multidisciplinary treatment of malignant melanoma, especially in the head-and-neck region.

CONCLUSION

In summary, we treated three patients with primary malignant melanoma of the nose and paranasal sinus by various therapies, but satisfactory results were not observed. However, upon chemohormonal therapy including TAM, an anti-estrogen agent, the patients showed good responses.

REFERENCES

1. Creagan ET, Ingl JN, Green SJ (1980) Phase-II study of tamoxifen in patients with disseminated melanoma. Cancer Treatm Rep 64: 166-201.
2. Del Prete SA, Maurer LH, O'Donnell (1984) Combination chemotherapy with cisplatin, carmustine, dacarbazine and tamoxifen in metastatic melanoma. Cancer Treatm Rev 68: 1403-1405.
3. Fisher RI, Nelfeld JP, Lippmann ME (1976) Estrogen receptors in human malignant melanoma Lancet 2: 337-338.
4. Fisher Rl, Young RC, Lippmann ME (1981) Diethylstilbestrol therapy of surgically non-resectable malignant melanoma. Proc Amer Assoc Cancer Res/ASCO 19: 339.
5. Hofmann J, Doppler W, Jakob A (1988) Enhancement of the antiproliferative action of CDDP and nitrogen mustard by inhibitors of protein kinase C. Int J Cancer 42: 382-388.
6. Lee SP, Shimizu KT, Tran LM (1994) Mucosal melanoma of the head and neck. The impact of local control on survival. Laryngoscope 104: 121-126.
7. Lund VJ (1993) Malignant melanoma of the nasal cavity and paranasal sinuses. ENT Journal 72: 285-290.
8. Mann SP, Andrew DA, Howell, SB (1989) Modulation of cisplatin accumulation by forskolin in human ovarian carcinoma cells. Proc Amer Assoc Cancer Res 30: 1851.
9. Masiel A, Buttrick P, Bitran J (1981) Tamoxifen in the treatment of malignant melanoma. Cancer Treatm Rep 65: 531-532.
10. McClay EF, Nasarangelo MJ, Bread D (1992) Effective combination chemohormonal therapy for malignant melanoma. Int J Cancer 50: 553-556.
11. McClay EF, Albright KA, Jones, JA (1993a) Tamoxifen modulation of cisplatin resistance in patients with metastatic melanoma: A biologically important observation. Cancer 72: 1914-1918.
12. McClay EF, Christian R, Albright KA (1993b) Tamoxifen modulation of cisplatin cytotoxity in human malignancies. Int J Cancer 55: 1018-1022.
13. Mirimanoff RO, Wagenknecht L, Hunziker, L (1981) Long-term complete remission of malignant melanoma with tamoxifen. Lancet 1: 1368-1369.
14. Nesbit RA, Woods RL, Tatrersall MH (1979) tamoxifen in malignant melanoma. N Eng J Med 301: 1241.
15. Papac R, Luikhart S, Kirkwood J (1980) High dose tamoxifen in patients with advanced renal cell cancer and malignant melanoma. Proc Amer Assoc Cancer Res/ASCO 21: 34.

Wataru Seo
Department of Otorhinolaryngology
Hyogo College of Medicine
1-1 Mukogawa, Nishinomiya
Hyogo 663
Japan