Recurrent and metastatic clivus chordoma: systemic palliative therapy retards disease progression

Katharina Schönegger[a,b], Ellen Gelpi[b], Daniela Prayer[c], Karin Dieckmann[d], Christian Matula[e], Marco Hassler[a], Johannes A. Hainfellner[b] and Christine Marosi[a]

We report on a male patient with progressive and metastatic clivus chordoma treated over a period of 9 years by a multidisciplinary approach. Within the first 4 years, the patient underwent surgery four times. Thereafter, he received radiotherapy and subsequent chemotherapy. Stabilization of disease was achieved repeatedly for variable periods under local radiotherapy, systemic chemotherapy, immunomodulatory and anti-angiogenic therapy with isotretinoin and interferon-α, followed by thalidomide. Due to the occurrence of brain and lung metastases 8 years after initial diagnosis, liposomal doxorubicin was added to thalidomide. At the last follow-up control the patient had stable disease, with no progression of the intracranial tumor and regression of pulmonary metastases. He is in a good physical, psychological and neurological condition with a Karnofsky score of 80. Our observations show that multimodal therapy including a systemic palliative approach is associated with long quiescent intervals in recurrent chordoma and with regression of its metastases. Use of substances with high efficacy on tumor tissue and low toxicity, allowing long-term administration, seems promising in similar situations. ***Anti-Cancer Drugs*** **16:1139–1143 © 2005 Lippincott Williams & Wilkins.**

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[a]Clinical Division of Oncology, Department of Medicine I, [b]Institute of Neurology, [c]Department of Neuroradiology, [d]Department of Radiooncology and [e]Department of Neurosurgery, Medical University Vienna, General Hospital (AKH), Vienna, Austria.

Correspondence to C. Marosi, Clinical Division of Oncology, Department of Medicine I, Medical University Vienna, 1090 Vienna, Austria.
Tel: +43 1 40400 4429; fax: +43 1 40400 4451;
e-mail: christine.marosi@meduniwien.ac.at

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Introduction

Clivus chordomas are rare tumors of the skull base that are thought to originate from embryonic remnants of the primitive notochord – a primitive structure around which the skull base and vertebral column develop. Therefore, chordomas are found in those areas (saccrococcygeal, spheno-occipital, vertebral) where vestiges of this tissue remain.

Chordomas account for 0.2% of brain tumors and they may occur at any age, with a peak prevalence in the fourth decade of life. There is a male preponderance of 2:1 for all chordomas [1,2]. They are malignant, slowly growing, but locally aggressive tumors, eroding and destroying bone. Intracranial chordomas usually do not invade brain tissue, but they displace and compress it. Two histopathological subtypes are described. (i) The typical chordoma: its cells are arranged in cords in a pale mucopolysaccharide matrix with a characteristic physaliphorous appearance. (ii) The chondroid chordoma: its stroma resembles hyaline cartilage with neoplastic cells in lacunae. This type resembles low-grade chondrosarcoma and can be distinguished with the help of immunohistochemical markers [3].

Intracranial chordomas most frequently present with diplopia, headache, ataxia and other signs of cranial nerve palsies [4]. Distant metastases occur in 7–14% of the cases, most frequently affecting lung, liver, bone or lymph nodes [5,6].

In our study we report on a patient with a progressive and metastatic clivus chordoma treated over a period of 9 years by neurosurgery, radiotherapy, chemotherapy, immunomodulatory and anti-angiogenic therapy, leading to retardation of disease progression.

Case presentation

The long and troublesome case history of our 51-year-old patient started with difficulties in breathing through his nose approximately 10 years ago. In 1995, a tumor was detected in the epipharynx. On the magnetic resonance imaging (MRI) scan, the extent of the tumor, which had its origin in the clivus and infiltrated the sinus sphenoidales, was visible (see Fig. 3a). Complete tumor resection was performed at the Department of Neurosurgery at the Medical University of Vienna, Austria. Histopathologically, a chondroid chordoma was confirmed (see Fig. 1). In

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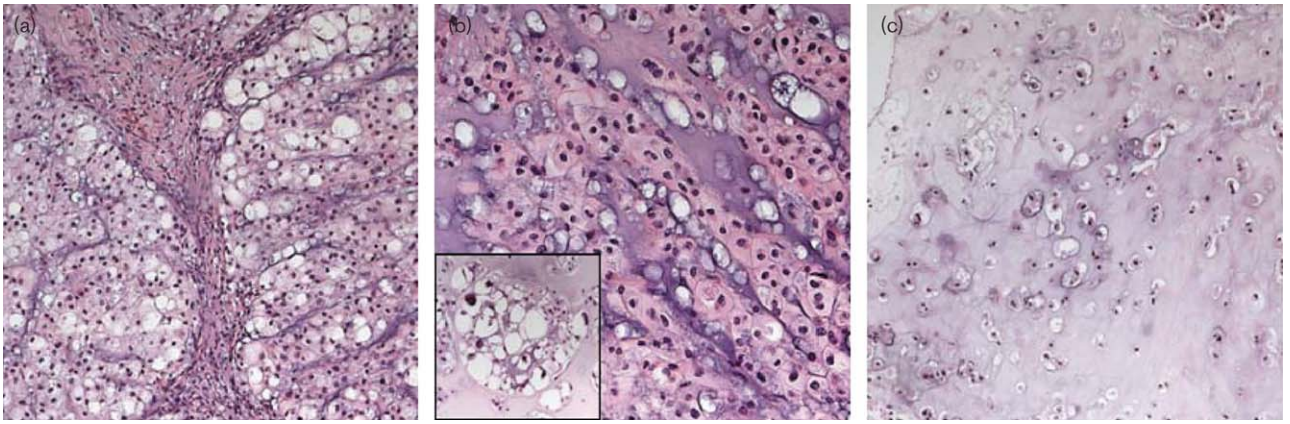
this first specimen the MiB-1 tumor cell proliferation index was 5%.

One year later in a control computed tomography scan, a local recurrence of the chordoma in the sinus outspreading in both nasal cavities was the cause for a second resection.

Two years later, symptoms of nasal constriction again led to a third resection. In 1999, a compression of the right arteria carotis interna and an infiltration of the sinus cavernosus caused acute blindness of both eyes. Acute neurosurgical decompression of the arteria carotis and debulking was performed in order to save the right nervous opticus could not save the vision of the right eye (see Figs 2a, 2b, 3b and 3c). Plain histology in the specimen of the last surgery showed similar characteristics as at first histological diagnosis, but revealed an increased mitotic activity with a MiB-1 tumor cell proliferation index of 20%. The patient underwent radiotherapy with 59.1 Gy focused on the clivus, the epipharynx and the sinuses. The radiotherapy induced a moderate reduction of the residual tumor mass.

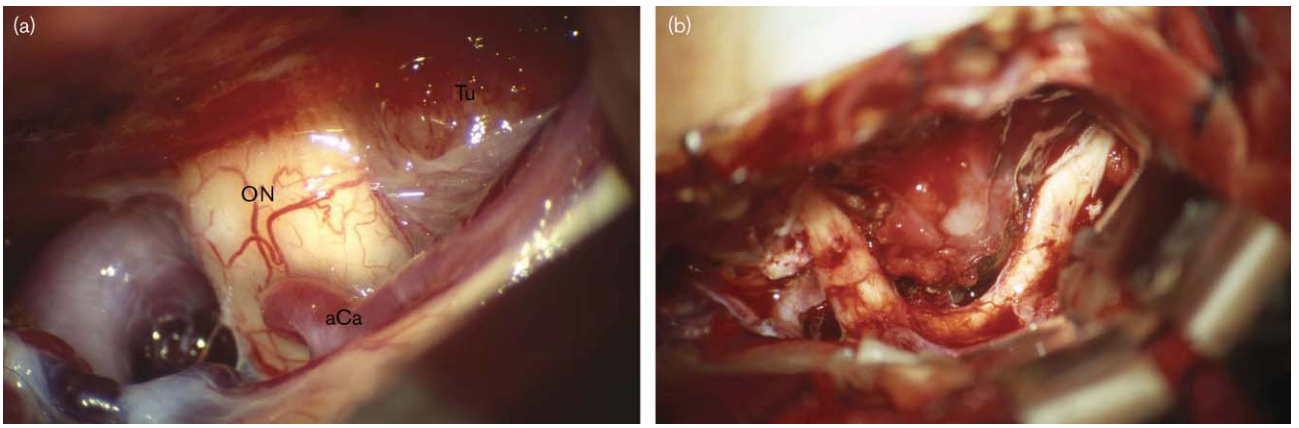
In July 2000, after local progression, the patient was referred to the Medical Department of Oncology for the initiation of a palliative chemotherapy. The first scheme regarded as suitable was EVAIA (etoposide 150 mg/m^2 on

Fig. 1



(a) Plain histology shows the lobular architecture of tumor tissue: solid tumor formations are separated by mesenchymal stroma (H & E ×100). (b) Higher magnification shows rows and cords of epithelial tumor cells embedded in a myxoid matrix. The inset shows a physalophorous cell (H & E ×200, inset ×400). (c) Chondroid differentiation as seen in small tumor areas (H & E ×100).

Fig. 2



(a) October 1999: intraoperative aspects after performing a left-sided approach. The left optic nerve can be clearly visualized compressed by an anatomical various loop of the left anterior communicating artery and by the tumor itself. ON, optic nerve; aCa, anterior communicating artery; Tu, tumor. (b) October 1999: during the same surgical procedure. Situation after decompression of the optochiasmal system. The suprasellar parts of the tumor have been removed and both optic nerves are decompressed.

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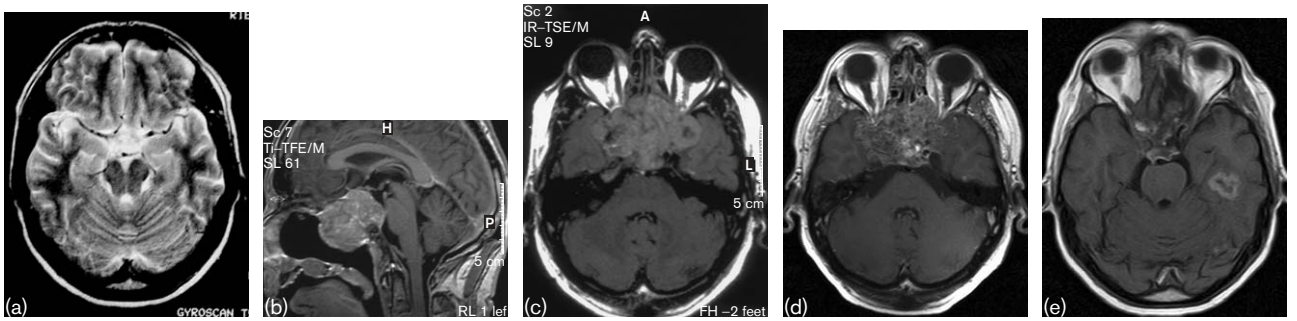
Fig. 3



(a) September 1995, before the first surgical intervention: axial T_1-weighted image after contrast media administration, irregular shaped tumor destroying the clivus. (b) October 1999: sagittal T_1-weighted image after contrast media administration. Large space-occupying lesion destroying the clivus, bulging equally into the prepontine cistern and the epipharynx. (c) Axial flair image from October 1999 of the recurred clivus chordoma. (d) February 2003: axial T_1-weighted image after contrast media application. Tumor relapse showing the lesion extending to both temporal lobes, to the prepontine cistern and the ethmoidal bone. (e) April 2004: axial T_1-weighted image after contrast media application, Post-therapeutically marked reduction of the original lesion, ring-shaped enhancing structure in the left temporal lobe.

day 1–3, ifosfamide 2000 mg/m^2 on day 1–3, doxorubicin 20 mg/m^2 on day 1–3 and vincristine 2 mg/m^2 on day 1). After the second cycle of EVAIA the patient developed severe toxicities grade III and IV (leukocytopenia, anemia and stomatitis) which forced us to stop this regimen. One month after the recovery from toxicity, in September 2000, a new approach was started with isotretinoin (Roaccutan; 30 mg/day) and interferon (IFN)-α (Intron A; 5 Mio/3 times a week), which was well tolerated. The patient was in a stable state of disease for approximately 1 year.

In November 2001, progression made it necessary to re-irradiate the tumor with 60 Gy, fractionated in 2 Gy ED per day focused on the palate and the upper anterior maxillary, while the isotretinoin/IFN-α therapy was continued. The drugs were stopped because of mucositis and anemia, while the radiotherapy was maintained to completion.

After stereotactic irradiation of an occipital brain metastasis with 18 Gy, a thalidomide-based therapy was initiated in February 2002. Again the tumor growth could be kept down for 1 year before the MRI control scan showed progression (see Fig. 3d). At that time pulmonary metastases were detected in the right lobe in a conventional X-ray (March 2003).

As a further neurosurgical intervention was not indicated because of the generalization of the tumor, the patient received five stereotactic irradiations (total 25 Gy) to the frontal basis followed by a new chemotherapeutic scheme: a combination of thalidomide 100 mg daily in the evening and liposomal doxorubicin (Caelyx) i.v. every 3 weeks. The patient received 12 cycles. The initial dose of liposomal doxorubicin was 25 mg/m^2 increased to 35 mg/m^2 after the first cycle. During the whole period the patient tolerated the chemotherapy well and developed no cardiac toxicity.

In June 2004, a new temporal brain metastasis observed in a control MRI was treated by stereotactic irradiation (see Fig. 3e). Currently, the patient is in a stable state, with no progression of the intracranial tumor and regression of the pulmonary metastases. In the case of iterated progression, the administration of imatinib mesylate is planned. After all interventions by neurosurgeons, neurooncologists and radiation oncologists, the patient is able to act autonomously and independently in his everyday life. Apart from the blindness in his right eye and the reduced vision in his left, the patient is in a good physical and psychological condition, as could be ascertained in a neurological examination (Karnofsky score 80).

Discussion

Local tumor control is of utmost importance in the treatment of intracranial chordoma. Complete surgical removal is the first and indispensable step [7]. The extension of the tumor through the skull base, its occurrence in relatively inaccessible sites and the fact that chordomas are not encapsulated with clear cleavage lines are often limiting factors with regard to the extent of tumor resection. Furthermore, an increase of tumor cell proliferation from primary to recurrent lesion in clivus chordoma as described by Naka *et al.* [8] reflects the progression of disease. These difficulties are the cause of multiple local recurrences and repeat surgical approaches, as was the case in our patient [9,10].

In case of incomplete resection, residual tumor can be successfully treated with radiation therapy. The combined treatment of surgery and irradiation achieves a 65%

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recurrence-free, 5-year survival rate [6]. As local tumor control could not be achieved in our patient with repeated surgery, radiation was started after the fourth recurrence and subsequent adjuvant chemotherapy was started.

An optimal chemotherapy regimen for chordomas has not yet been defined. In the literature, single-agent chemotherapy for chordomas has been reported as ineffective. There are only few reports of combined chemotherapies with questionable therapy success [11].

As chordomas are located in bones, their treatment with sarcoma therapy protocols seems logical.

We initiated chemotherapy in our patient using the EVAIA protocol. This combination chemotherapy for sarcomas is similar to the CYVADIC protocol previously applied by Karakousis *et al.* who could achieve a 30-month disease-free period for their patient [12]. Our patient developed severe toxicities and we had to stop chemotherapy after the second cycle. Looking for less burdening alternatives, we decided to use isotretinoin combined with IFN-α, which is a commonly used maintenance therapy for sarcomas with a low toxicity range [13,14]. Using this therapy, disease was stabilized for approximately 12 months.

Due to local progression of disease and side-effects under local irradiation of a cerebral metastasis, anti-angiogenic therapy with thalidomide was initiated. Thalidomide has demonstrated good results in the palliative treatment of primary brain tumors such as gliomas [15]. Its high permeability through the blood–brain barrier predisposes thalidomide for its use in the treatment of intracranial tumors. Patients with a long case history, as described above, can profit from a broad spectrum of effects, including its palliative and anticancer activity [16,17]. In our case, thalidomide was associated with disease stabilization for a duration of 1 year before pulmonary metastases and local intracranial tumor progression became evident.

Liposomal doxorubicin was added to the ongoing thalidomide therapy. Doxorubicin-based adjuvant chemotherapy for localized and resectable soft-tissue sarcomas significantly prolongs the time to local and distant relapse, and overall recurrence-free survival [18]. Patients reported in the chordoma literature as responsive to chemotherapy received anthracyclines as part of their therapy protocols [12,19–21]. Liposomal doxorubicin was shown to cause fewer side-effects (e.g. cardiac toxicity) and has better pharmacokinetic properties due to its accumulation in highly vascularized tumor tissue, leading to an increased tumor response [22]. The administration of 12 courses of this combination led to a regression of the pulmonary metastases. In case of iterated progression, imatinib mesylate will be administered according to the promising results from Casali *et al.* [23].

Whether adjuvant chemotherapy of chordoma results in a better long-term outcome cannot be proven by single case studies. Progressive and metastatic disease in the case of chordoma definitely requires systemic therapy. The systemic approach, in addition to local tumor control with surgery and radiation, can result in an optimal multimodal therapy with prolongation of quiescent intervals. Fagundes *et al.* introduced the term salvage therapy in recurrent and progressive chordoma with chemotherapy as part of it [24]. The applicability of systemic therapies in this rare tumor entity should be discussed again as there is no therapeutic standard defined for progressing cases. We support the use of substances with high tolerability, efficacy and low toxicity such as thalidomide/liposomal anthracycline or isotretinoin/IFN-α which can be administered over a long period.

Because of the rarity of chordoma and lack of data concerning systemic therapy concepts, future patients should be treated according to a consensus protocol.

Conclusion

Progressive and metastasizing chordoma requires systemic palliative therapy, in addition to local tumor control by surgery and radiotherapy. Observations in our patient indicate that multimodal therapy including a systemic palliative approach achieves long quiescent intervals in recurrent chordoma and regression of its metastases. Use of substances with high efficacy on tumor tissue and low toxicity allowing long-term administration seems reasonable. As the literature does not infer a particular systemic therapy, standard regimens still need to be defined.

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