Targeting the mammalian target of rapamycin in myxoid chondrosarcoma

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Myxoid chondrosarcoma is a slow-growing sarcoma poorly responsive to chemotherapy and radiation therapy. Translational research has validated several proteins as optional therapeutic targets. Significant responses are, however, rare. In this paper we report an extraordinary response of myxoid chondrosarcoma to targeted therapy by rapamycin in combination with cyclophosphamide. Our case points to a possible novel therapeutic approach towards myxoid chondrosarcoma, by targeting the mammalian target of rapamycin protein, and probably protein kinase C-α, mitogen-activated protein kinase, and Jun *N*-terminal kinase too, by rapamycin. *Anti-Cancer Drugs* 19:1019–1021 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Myxoid chondrosarcoma occurs most frequently in patients older than 35 years. The tumor characteristically shows a growth pattern of cells in a myxoid matrix. In contrast to the more common skeletal chondrosarcoma of bone, mature cartilage is unexpected. This tumor usually grows slowly, but late recurrence and metastasis are common, and this rate seems to be greater for extraskeletal than for skeletal variants [1]. The treatment of primary, recurrent or metastatic chondrosarcoma is wide resection, when feasible, whereas chemotherapy and radiation therapy have little effect on disease control. Translational research has validated platelet-derived growth factor receptor, estrogen signaling, matrix metalloproteinase-1, histone deacetylase, methylthioadenosine phosphorylase, and vascular endothelial growth factor (VEGF)-A as potential therapeutic targets [2]. Significant responses are still rare. In this paper we report an extraordinary response of myxoid chondrosarcoma to targeted therapy by rapamycin in combination with cyclophosphamide.

Case presentation

A 49-year-old woman underwent resection of a tumor of the 9th and 10th left ribs on 31 August 2003. The tumor was a 7.5-cm moderately differentiated (grade II/III) myxoid chondrosarcoma, resected with free margins. She had no adjuvant therapy and was free of disease until July 2005. At this stage lung metastases were incidentally found while preparing for repair of a surgical scar hernia. On 30 July 2005 she underwent right thoracotomy and five metastases of myxoid chondrosarcoma were removed. As part of her follow-up investigation, PET computed tomography (CT) was performed on 27 May 2006. It showed multiple right lung and pleural opacities without significant fluorodeoxyglucose uptake. At this point she was referred for a consultation at our clinic.

Her CT scan (4 July 2006) showed multiple bilateral lung lesions measuring 2–24 mm. The case was discussed by a multidisciplinary team, which defined the disease as inoperable. As standard chemotherapy for sarcomas is usually ineffective in chondrosarcoma, we proposed to her an experimental approach with gemcitabine or best supportive care. Between 10 September 2006 and 29 October 2006 she received gemcitabine weekly. On the CT scan from 1 November 2006 there was clear progression of the disease; but as the patient reported significant clinical improvement (less dyspnea, cough and pain), the treatment was continued for an additional 2 months. On CT from 15 January 2007 additional progression of disease was observed – the nodules grew to 53 mm. The treatment was replaced by vinorelbine weekly, but the disease progressed further. Clinical deterioration of the patient, manifested by chest pain, cough, and dyspnea was also observed. Chest plain film was obtained on 16 April 2007 as a baseline for a new approach by oral cyclophosphamide (200 mg/day D1–7, 15–21 + oral rapamycin 3 mg/day D1–21 Q28d). At her visit after two courses of treatment the patient reported symptomatic improvement. The CT scan from 10 June 2007 was surprising – some of the nodules remained stable, others had become smaller. The patient resumed her daily life activities. We recommended continuation of the treatment. At her August visit she reported new skeletal pain, burning feeling at the chest wall, and

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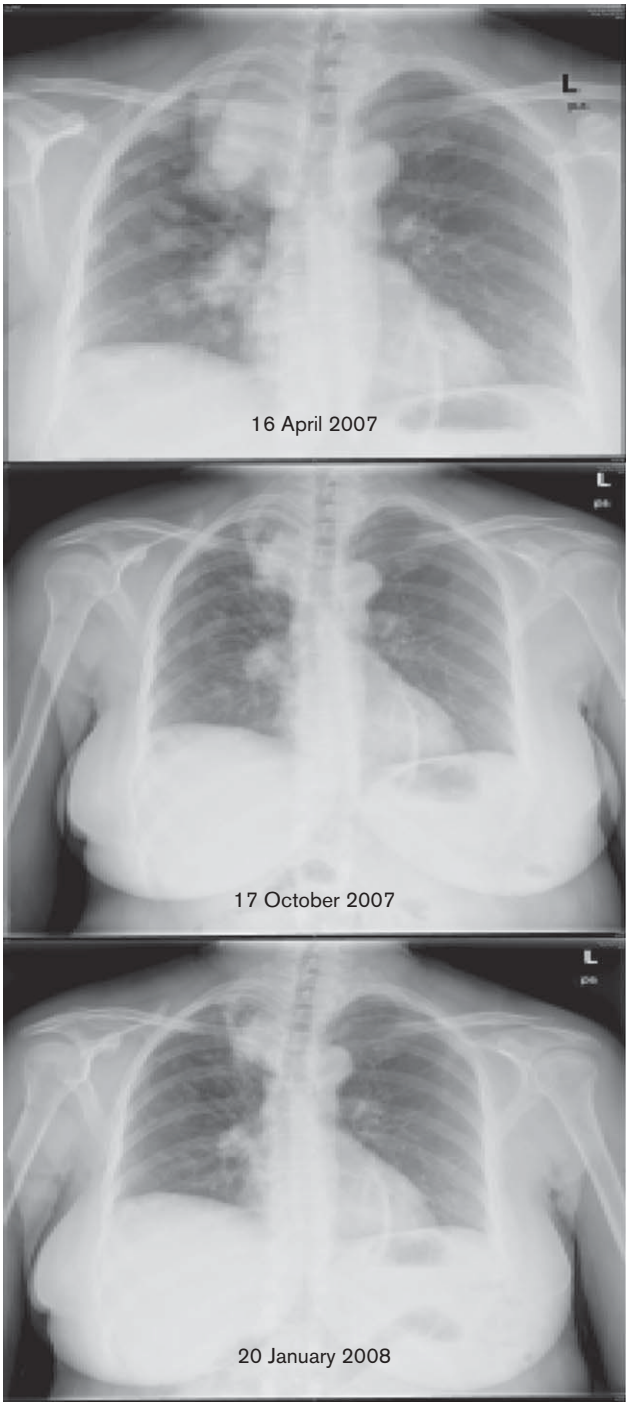
dryness of eyes and skin, but her performance status was 0–1. Bone scan (13 August 2007) was normal and she continued treatment for another month. On 17 October 2007 plain chest film, a good partial response was observed. The patient resumed her sportive activities. The therapy was continued with symptomatic treatment of the side effects (antibiotics for UTI, antiacneic creams, steroid paste for mucositis, zinc and magnesium for nail problems). At her last visit on January 2008, the plain chest film showed additional shrinkage of most of the nodules (Fig. 1). Complaints of periodic pain in the chest wall and dry eyes are still observed, but no functional disturbance.

Fig. 1



Plain chest film follow-up of chondrosarcoma metastases approached by oral rapamycin and oral cyclophosphamide. Plain chest film demonstrated the extent of disease in a single view better than serial chest computed tomography cuts.

Discussion

Potential molecular targets in mesenchymal chondrosarcoma have been already explored [2,3] utilizing a proteomic approach. Malignant mesenchymal chondroblasts exhibited stronger expressions of CD99, IL-1-α, conventional protein kinase C (PKC)-α, phosphorylated PKC-α/β, platelet-derived growth factor receptor-α, phosphorylated Jun *N*-terminal kinase (JNK), Ki-67, bcl-2, and mammalian target of rapamycin (mTOR) antigens than their more mature-appearing chondrocytic counterparts in myxoid chondrosarcoma [3,4]. Increasing evidence suggests a role of mTOR targeting in cancer therapy, with or without chemotherapy [5,6]. Sirolimus (rapamycin) is a macrocyclic triene antibiotic that inhibits activation of S6 kinase, the cyclin-dependent kinase (CDK) 2/cyclinE complex and phosphorylation of retinoblastoma (Rb) protein and causes cell cycle arrest in G1-S phase. Through its highly selective binding to its intracellular receptor protein FKBP12, rapamycin forms a complex that inhibits the function of the signaling kinase 'mTOR' [7]. The latter belongs to the family of phosphatidylinositol-3-kinase-related kinases, which are involved in the control of essential cell functions, including cell cycle progression, cell cycle check points, DNA repair, and DNA recombination [8]. Specifically, mTOR, is a downstream component in the phosphatidylinositol-3-kinase/Akt (protein kinase B) pathway, which participates in the transduction of signaling events ultimately linked to the activation of CDKs, increase in the cellular levels of cyclins such as cyclin D1, and phosphorylation of the Rb protein. As such, mTOR plays a central role in the control of cell proliferation, cell survival, and adhesion-independent survival and migration [9,10]. Through the inhibition of mTOR, rapamycin causes cell cycle arrest in the G1 phase, prevents CDK activation, inhibits Rb protein phosphorylation, and accelerates the turnover of cyclin D1, leading to a deficiency of active CDK4/cyclin D1 complexes. These events then contribute to the prominent inhibitory effects of rapamycin at the G1/S boundary of the cell cycle [11]. Notably, rapamycin also displays antiangiogenic activities linked to a decrease in the production of VEGF thereby markedly inhibiting response of vascular endothelial cells to stimulation by VEGF [12]. The various effects of rapamycin may be dose-related [13]. Specifically, in chondrosarcoma, rapamycin blocks the

pathway of PKC-α and p38 mitogen-activated protein kinase, leading to the inhibition of chondrogenesis of mesenchymal cells [14]. In addition, rapamycin reduces JNK activity and thus may be targeted as a therapeutic strategy [15]. The role of cyclophosphamide in combination with rapamycin is unclear at present. In conclusion, this is a rare success of treating metastatic chemoresistant chondrosarcoma orally by rapamycin and cyclophosphamide. Our case points to a possible novel therapeutic approach toward myxoid chondrosarcoma, by targeting mTOR protein, and probably also PKC-α, mitogen-activated protein kinase and JNK, by rapamycin. A phase II study of rapamycin in patients with chondrosarcoma is warranted.

Dedication

This article is dedicated to the memory of Dr Avner Eisenberg.

References

1 Brennan M, Singer S, Maki RG, O'Sullivan B. Sarcomas of the Soft Tissues and Bone: section 1: soft tissue sarcoma. In: Vincent T, DeVita SH, Steven Rosenberg A, editors. *Cancer Principles & Practice of Oncology* Edition. Philadelphia: PA Lippincott Williams & Wilkins; 2000.

2 Chow WA. Update on chondrosarcomas. *Curr Opin Oncol* 2007; **19**:371–376.

3 Brown RE, Boyle JL. Mesenchymal chondrosarcoma: molecular characterization by a proteomic approach, with morphogenic and therapeutic implications. *Ann Clin Lab Sci* 2003; **33**:131–141.

4 Brown RE. Morphoproteomic portrait of the mTOR pathway in mesenchymal chondrosarcoma. *Ann Clin Lab Sci* 2004; **34**:397–399.

5 Merimsky O. Targeting metastatic leiomyosarcoma by rapamycin plus gemcitabine: an intriguing clinical observation. *Int J Mol Med* 2004; **14**:931–935.

6 Merimsky O, Gorzalczany Y, Sagi-Eisenberg R. Molecular impacts of rapamycin-based drug combinations: combining rapamycin with gemcitabine or imatinib mesylate (Gleevec) in a human leiomyosarcoma model. *Int J Oncol* 2007; **31**:225–232.

7 Chen J, Zheng XF, Brown EJ, Schreiber SL. Identification of an 11-kDa FKBP12-rapamycin-binding domain within the 289-kDa FKBP12-rapamycin-associated protein and characterization of a critical serine residue. *Proc Natl Acad Sci U S A* 1995; **92**:4947–4951.

8 Keith CT, Schreiber SL. PIK-related kinases: DNA repair, recombination, and cell cycle checkpoints. *Science* 1995; **270**:50–51.

9 Huang S, Bjornsti MA, Houghton PJ. Rapamycins: mechanism of action and cellular resistance. *Cancer Biol Ther* 2003; **2**:222–232.

10 Chen J. Novel regulatory mechanisms of mTOR signaling. *Curr Top Microbiol Immunol* 2004; **279**:245–257.

11 Mita MM, Mita A, Rowinsky EK. Mammalian target of rapamycin: a new molecular target for breast cancer. *Clin Breast Cancer* 2003; **4**:126–137.

12 Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, *et al*. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med* 2002; **8**:128–135.

13 Guba M, Koehl GE, Neppl E, Doenecke A, Steinbauer M, Schlitt HJ, *et al*. Dosing of rapamycin is critical to achieve an optimal antiangiogenic effect against cancer. *Transpl Int* 2005; **18**:89–94.

14 Oh CD, Kim SJ, Ju JW, Song WK, Kim JH, Yoo YJ, Chun JS. Immunosuppressant rapamycin inhibits protein kinase C alpha and p38 mitogen-activated protein kinase leading to the inhibition of chondrogenesis. *Eur J Pharmacol* 2001; **427**:175–185.

15 Ishizuka T, Sakata N, Johnson GL, Gelfand EW, Terada N. Rapamycin potentiates dexamethasone-induced apoptosis and inhibits JNK activity in lymphoblastoid cells. *Biochem Biophys Res Commun* 1997; **230**:386–391.