

The effects of ciprofloxacin and paclitaxel on metastatic and recurrent chondrosarcoma

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Currently, the only treatment available for recurrent/metastatic chondrosarcoma is further surgical resection. Fluoroquinolones have shown toxicity in immature cartilage, inducing apoptosis and inhibiting the proliferation of human chondrosarcoma cells. Since previous studies suggested that ciprofloxacin and paclitaxel act synergistically in slowing the growth of chondrosarcoma in vitro, we investigated their effects on human recurrent/metastatic chondrosarcoma. Four patients received oral ciprofloxacin (750 mg twice daily) and intravenous paclitaxel (90 mg/m²) for 6–8 weeks of each cycle. Patient 1 remained stable 32.8 weeks after initiation of treatment. Patient 2 showed a 60% decrease in tumor growth but progressed by 10.3 weeks. Patient 3 progressed over 9 weeks, remained stable for 16 months, and then progressed after treatment with paclitaxel was discontinued. Patient 4 had three lesions: the recurrent lesion progressed despite treatment, showing an 8% increase in growth; one metastatic lesion remained stable (18 weeks), and the second metastatic lesion progressed. Gene expression profiling of normal articular cartilage and human chondrosarcoma cells exposed to ciprofloxacin showed differential expression of the genes *DDX5*, *MYST2*, *ISGF3*, *APC*, *RPL3*, *EIF4G2*, and *ERH*, all of which are involved in cell proliferation, cell-cycle regulation, or apoptosis.

The majority of chondrosarcomas are classified as low-grade malignant tumors and exhibit a lower rate of metastasis than do other sarcomas.¹ The front-line treatment—and currently the only effective therapy—for chondrosarcoma is surgical resection, which is often curative. However, metastases and local recurrences do develop and are particularly problematic since there is no acceptable treatment beyond further attempts at resection.

Clinical and in vitro studies have demonstrated that fluoroquinolones are toxic to immature, but not mature, animal chondrocytes.^{2–7} Although the exact mechanism of fluoroquinolone arthropathy is unknown, several molecular mechanisms for fluoroquinolone chondrotoxicity have been proposed. Studies have shown that healthy human chondrocytes and chondrocytes within enchondromas develop normally in vitro when exposed to ciprofloxacin, whereas human chondrosarcoma chondrocytes show a dramatic dose-related response to fluoroquinolones, displaying immunohistochemical evidence of induced apoptosis.⁶

The chemotherapeutic mitotic inhibitor paclitaxel has proven effective in human malignancies

refractory to conventional chemotherapy.^{8–11} In vitro studies performed at this institution have shown that the combination of ciprofloxacin (Cipro) and paclitaxel appears to be synergistic, having the most dramatic cytotoxic effects on human chondrosarcoma chondrocytes, with little effect on normal or enchondroma chondrocytes. These in vitro results, produced by commonly used pharmaceuticals, suggested a promising chemotherapeutic approach to the treatment of chondrosarcoma.

We therefore undertook a clinical study to evaluate the effectiveness and safety of ciprofloxacin and paclitaxel for the treatment of recurrent and metastatic chondrosarcoma. We hypothesized that rates of tumor growth would decrease after initiation of the combination. We also hypothesized that ciprofloxacin may affect the genes involved in apoptosis, cell growth, and proliferation

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and consequently made a preliminary attempt to determine which genes were responsible in vitro.

Materials and methods

Institutional review board approval of the study was obtained, and all patients were informed and gave their consent. Inclusion criteria included a histologic diagnosis of chondrosarcoma with local recurrence or metastasis. Four patients were enrolled. Each patient received 750 mg of ciprofloxacin orally, twice a day, during an 8-week cycle and 90 mg/m² of paclitaxel intravenously, infused over 1 hour each week, for 6 weeks out of the 8-week cycle. Each patient's clinical history, the occurrence of side effects, and any changes in tumor size over the course of treatment were recorded.

Response to chemotherapy was measured using the World Health Organization classification for solid tumors.¹² *Complete response* was defined as complete tumor regression for ≥ 4 weeks, *partial response* as $\geq 50\%$ reduction in tumor cross-sectional area for ≥ 4 weeks, *progressive disease* as an increase in tumor cross-sectional area $\geq 25\%$ or the appearance of new lesions, and *stable disease* as disease not satisfying the definition of complete response, partial response, or progressive disease. Tumor cross-sectional areas were calculated from magnetic resonance imaging (MRI) or computed tomographic (CT) scans. In addition, the growth rates of tumors before, during, and—in one patient—after treatment with ciprofloxacin and paclitaxel were determined from the slope of a best-fit line calculated according to the method of least squares and were compared in each patient. The small patient numbers precluded statistical analysis.

For our in vitro study, normal articular cartilage and chondrosarcoma cells obtained from surgical specimens were grown in suspension culture for 3 days and then ex-

posed to 5 or 10 mg/L of ciprofloxacin for 24 hours. (A concentration of 5 mg/L was chosen because it approximates the mean arterial concentration seen in patients taking the drug.) Following ciprofloxacin treatment, total RNA was extracted and converted in vitro to cDNA or complementary RNA. The sample was then biotinylated, fragmented, and hybridized to an Affymetrix (Santa Clara, CA) U133 GeneChip. Following hybridization, the chip was washed, labeled with fluorescent dye, and scanned. The data were then imported to GeneSifter for gene expression analysis. As a control, untreated cartilage was compared with ciprofloxacin-treated cartilage. For the purposes of this study, we increased the threshold for differential expression to $P < 0.005$ and concentrated on genes known to be involved in cell growth, cell-cycle regulation, and apoptosis.

Results

Patient 1

Patient 1 is a 25-year-old male who was diagnosed with grade 2 extraskeletal chondrosarcoma of the scapula in 2001. The scapular le-

sion was treated surgically with a wide resection of the tumor, including partial resection of the scapula. Margins were negative. A local recurrence was found 1 year postoperatively. The patient was treated with a radical resection of the scapula and replacement of the bone with a prosthetic scapula. Eighteen months after the initial diagnosis, multiple lung metastases (all < 1 cm in size) were found on a routine CT scan. At resection 4 months later, 23 of the 30 nodules were positive for low-grade metastatic chondrosarcoma.

The patient started ciprofloxacin in August 2003, receiving 250 mg daily for the first 2 months and 750 mg twice daily thereafter. Paclitaxel was added in March 2004, and 6 cycles have been administered to date. Side effects were mild and included neuropathy in both feet, mild nausea, and a slight change in taste.

One lung lesion was consistently described and measured on imaging before and after treatment. After the recurrence and before the addition of paclitaxel, this tumor was growing at a rate of 0.783 cm²/yr. After treatment with ciprofloxacin and paclitaxel was initiated, the tumor growth rate decreased by 90.7% to 0.073 cm²/

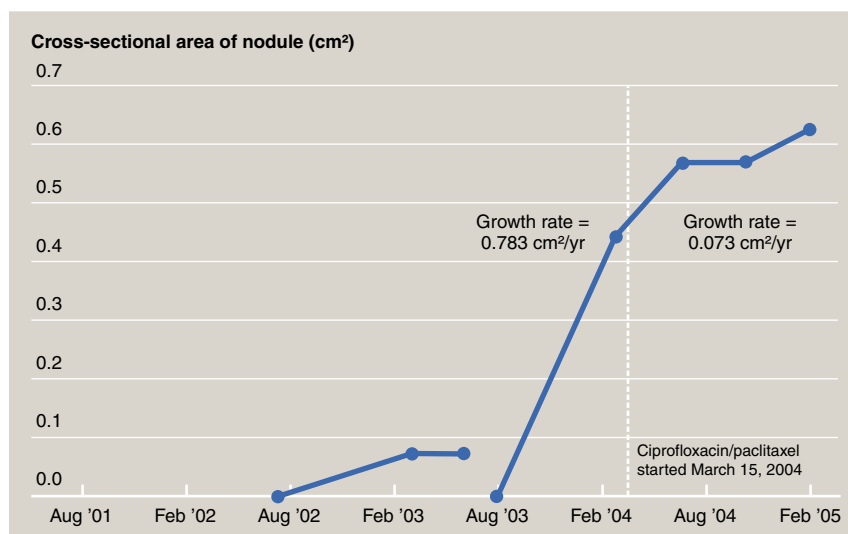


FIGURE 1 Changes in the size of patient 1's metastatic lung nodule over time. Tumor growth rates before and after initiation of treatment with ciprofloxacin and paclitaxel are shown.

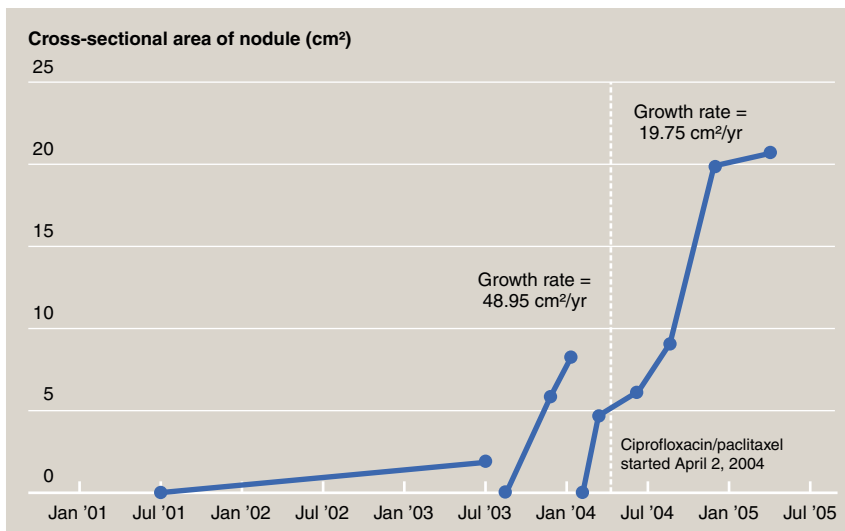


FIGURE 2 Changes in the size of patient 2's pelvic tumor over time. Tumor growth rates before and after initiation of treatment with ciprofloxacin and paclitaxel are shown.

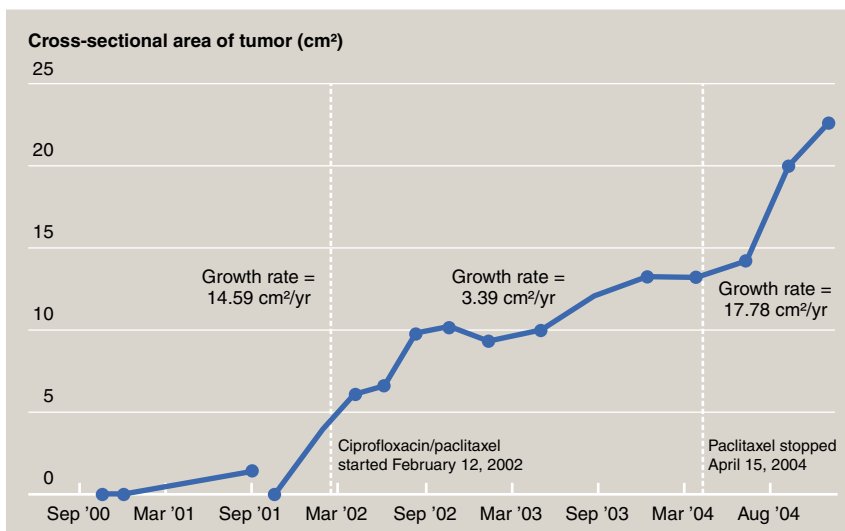


FIGURE 3 Changes in the size of patient 3's paraspinal tumor over time. Tumor growth rates before, during, and after treatment with ciprofloxacin and paclitaxel are shown.

yr (Figure 1). The patient has had stable disease for 8 months, with only a 9.6% increase in tumor size since initiation of treatment.

Patient 2

Patient 2 is a 45-year-old male with grade 1 chondrosarcoma of the pelvis, which was diagnosed in July 2001. He was treated with a right internal hemipelvectomy; margins were positive. A recurrence was diagnosed by MRI 26 months later, and he un-

derwent another resection. He started ciprofloxacin (750 mg twice daily) in October 2003. In February 2004, a second recurrence was found on MRI, and a partial resection was performed. Paclitaxel was added in April 2004, and 6 cycles have been administered to date. Side effects were mild, including neuropathy of the fingers and toes.

After the second recurrence and before treatment with paclitaxel, the tumor was growing at a rate of 48.95

cm²/yr. After treatment with both ciprofloxacin and paclitaxel was initiated, the growth rate decreased by 59.7%, to 19.75 cm²/yr (Figure 2). However, the tumor size increased 49% over 2 months and the patient was therefore classified as having progressive disease. Interestingly, the tumor growth rate decreased dramatically in the past 4 months, with the size of the tumor increasing only 3.3% during that time.

Patient 3

Patient 3 is a 60-year-old male who was diagnosed with grade 1/2 thoracic paraspinal chondrosarcoma in October 2000. Two months later, he underwent a surgical debulking. Ten months postoperatively, a laminectomy and partial excision were performed due to extradural compression of the spinal cord. Treatment with ciprofloxacin and paclitaxel was started in February 2002 and was continued for 26 months. Paclitaxel was stopped in April 2004 because the patient had stable disease and was asymptomatic, except for a severe distal neuropathy. Six months later, MRI showed progression. He underwent his third debulking in November 2004. There was no evidence of necrosis on histopathology. He is currently symptomatic with pain and has shown further progression.

Before treatment with paclitaxel, the tumor was growing at a rate of 14.59 cm²/yr. After initiation of treatment with ciprofloxacin and paclitaxel, the growth rate decreased to 3.39 cm²/yr (Figure 3). This was a 76.8% decrease in growth rate, but after 17 weeks of treatment, the size of the tumor had increased by 67%. The patient was therefore classified as having progressive disease. Thereafter, the growth of the tumor leveled off, and the patient has had stable disease for 16 months. After treatment with paclitaxel was discontinued, the growth rate rebounded to 17.78 cm²/yr, exceeding the growth rate before treatment.

Patient 4

Patient 4 is a 58-year-old male with grade 2 chondrosarcoma of the right ribs, which was diagnosed in 1994. Resection was performed in 1995 and again 2 years later for a local recurrence. Multiple pulmonary nodules (all < 1 cm in diameter) and one abdominal metastasis were noted on CT. The pulmonary nodules were resected in November 2001 and found to be well differentiated. Progression of the rib and lung lesions was noted

in October 2002. Ciprofloxacin and paclitaxel were started in May 2004, and the patient has undergone 4 cycles so far. Side effects have been mild and include neuropathy of the feet.

Not all of the measurements of the patient's rib lesion dating back to his last resection were available. However, those that were available show that, before treatment with ciprofloxacin and paclitaxel, the tumor was growing at a rate of 26.50 cm²/yr. After treatment with ciprofloxacin and

paclitaxel, the growth rate increased slightly to 28.69 cm²/yr (Figure 4), an 8.3% increase in growth rate. At 7 months, tumor size had increased by 37%, and the lesion was therefore classified as progressive.

One of the multiple lung nodules was consistently measured and reported in the imaging reports. This cardiophrenic lesion was growing at a rate of 4.89 cm²/yr. After treatment with ciprofloxacin and paclitaxel, the growth rate decreased to 0.84 cm²/yr (Figure 5), an 83% decrease in growth rate. This lesion is stable, with tumor size increasing at a rate of only 4.2% at 4.5 months.

Patient 4's abdominal metastatic lesion was growing at a rate of 8.18 cm²/yr prior to treatment with ciprofloxacin and paclitaxel. After treatment, the growth rate increased to 46.28 cm²/yr (Figure 6). This was an increase of 466%. In terms of numbers, this increase seems very large; however, the figure shows a gradual increase in growth rate over time. After 4 months of treatment, this lesion had grown 33% in size and was considered progressive.

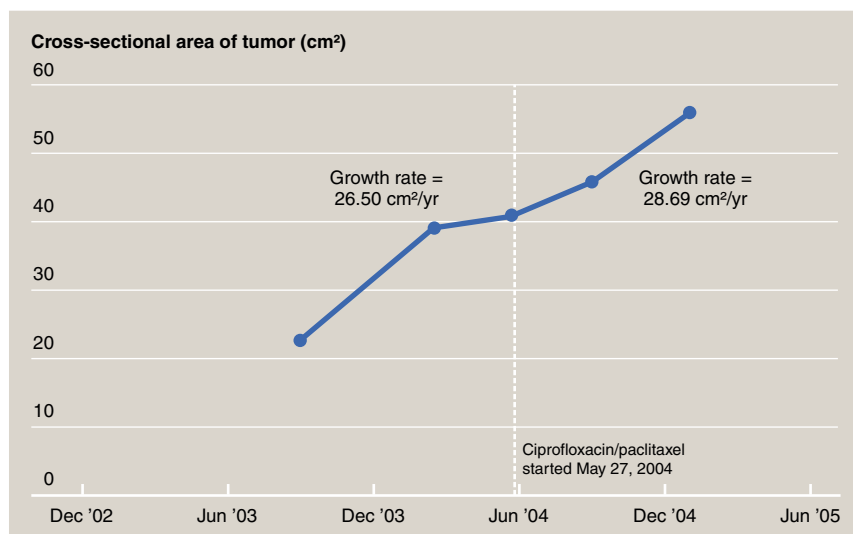


FIGURE 4 Changes in the size of patient 4's rib tumor over time. Tumor growth rates before and after initiation of treatment with ciprofloxacin and paclitaxel are shown.

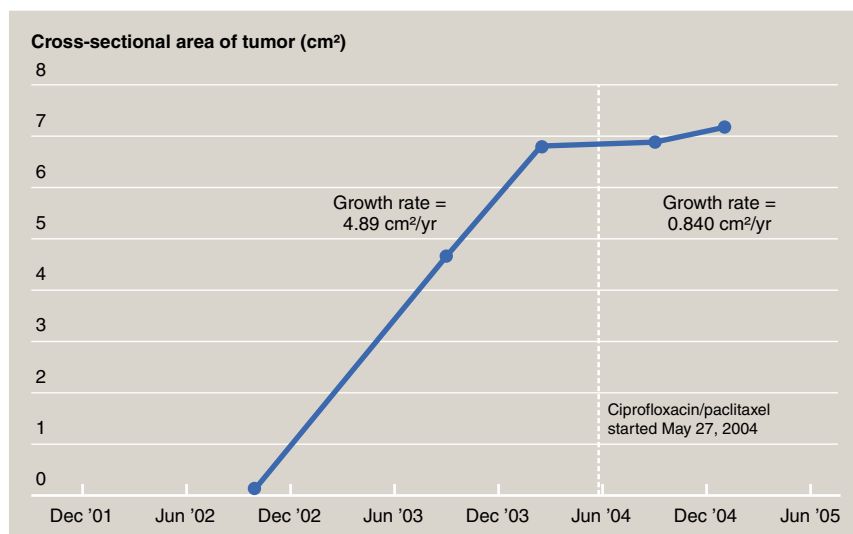


FIGURE 5 Changes in the size of patient 4's cardiophrenic lung metastasis over time. Tumor growth rates before and after initiation of treatment with ciprofloxacin and paclitaxel are shown.

Gene expression

In our in vitro testing, we found 950 genes that were differentially expressed ($P < 0.05$) in both our treatment and control groups. We increased our threshold for differential expression to $P < 0.005$ and found 111 genes that were differentially expressed. Of those, the genes known to be involved in cell growth, cell-cycle regulation, and apoptosis were *DDX5*, *MYST2*, *ISGF3*, *APC*, *RPL3*, *EIF4G2*, and *ERH*.

Discussion

Treatment options are limited for patients with chondrosarcoma recurrences and metastases. Currently, the only effective treatment is further surgical resection. We conducted this clinical study to determine whether the combination of ciprofloxacin and

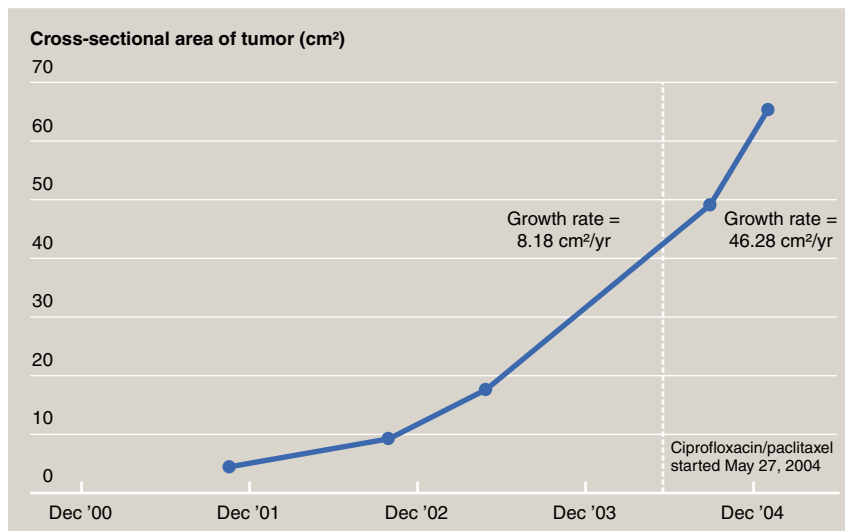


FIGURE 6 Changes in the size of patient 4's abdominal metastasis over time. Tumor growth rates before and after initiation of treatment with ciprofloxacin and paclitaxel are shown.

paclitaxel would be an effective treatment for recurrent and metastatic lesions. This report describes our early results in four patients, as well as our preliminary attempt to determine which genes may play a role in the apoptosis, growth inhibition, and decreased proliferation of cultured chondrosarcoma cells exposed to ciprofloxacin.

Background and rationale

In vitro studies previously performed at our institution added paclitaxel to ciprofloxacin because paclitaxel, which inhibits microtubule assembly,¹³ had shown promise in the treatment of malignancies resistant to standard chemotherapy. In addition, paclitaxel has been shown to be effective in the treatment of hormone-refractory prostate cancer^{9,10} and platinum-resistant ovarian cancer.⁸

Only one published study has examined the effects of paclitaxel on chondrosarcoma.¹³ This phase II study of paclitaxel, in which doses of 175–200 mg/m² were administered to 15 patients with previously treated osteosarcoma or a variant of the disease, showed a mixed response in 1 of the 2 patients with dedifferentiated chondrosarcoma. In this patient, a 1.5 × 1.3 cm metastatic lesion in the lungs

disappeared, whereas lesions in both hila progressed in size and number. No other responses occurred. These data support previous in vitro observations showing that paclitaxel has an effect on chondrosarcoma but little or no effect on osteosarcoma or liposarcoma.⁶ Only 1 out of 36 treatment cycles in 15 patients was complicated by febrile neutropenia. No other complications were reported.

The effects of ciprofloxacin on healthy and developing cartilage have been studied extensively.^{2–5,14–19} However, we are not aware of any studies, outside of those at our institution, regarding the effects of ciprofloxacin on chondrosarcoma.

Clinical observations

In our clinical study, using ciprofloxacin and paclitaxel together, we saw decreases in tumor growth rates in three patients and a mixed response in the fourth patient with a rib lesion and metastases to the abdomen and lungs. Patient 1, with lung metastases from a grade 2 extraskel-etal chondrosarcoma, experienced a 90.7% decrease in tumor growth rate after treatment with ciprofloxacin and paclitaxel was started and has had stable disease for 8 months. Pa-

tient 2, with recurrent grade 1 chondrosarcoma of the pelvis, responded at first with a 59.7% decrease in tumor growth rate but subsequently demonstrated progressive disease at 2 months. Patient 3, with recurrent paraspinal chondrosarcoma, initially showed a 76.8% decrease in growth rate; the disease then progressed and then remained stable for 16 months. After the patient discontinued paclitaxel, the tumor growth rate increased to pretreatment levels. Patient 4, with a grade 2 rib lesion and metastases to the lungs and abdomen, had an 8.3% increase, 83% decrease, and 466% increase in growth rates, respectively.

Although treatment of recurrent/metastatic chondrosarcoma with a combination of ciprofloxacin and paclitaxel did not induce a response in all lesions or in all patients, tumor growth rates did decrease considerably in most lesions. The sharply increased tumor growth rate seen in patient 3 after discontinuation of paclitaxel provides strong evidence that the reduction in tumor growth rate seen initially in this patient was due to treatment with this regimen, although it is not possible to determine if the response was due to paclitaxel, ciprofloxacin, or a synergistic effect of both drugs acting in concert. In regard to the regimen's relative safety, no instances of febrile neutropenia were observed, but each patient experienced some degree of distal neuropathy. One patient also had mild nausea and a change in taste sensation.

Molecular mechanisms for fluoroquinolone chondrotoxicity

In vitro, fluoroquinolones induce oxidative metabolism within immature or undifferentiated chondrocytes, leading to an impairment of proteoglycan and procollagen synthesis.²⁰ Fluoroquinolones such as ciprofloxacin produce disturbances in chondrocyte adherence, cytoskeletal changes, a reduction in the numbers of actin stress fibers,³ and changes in proteo-

glycan and fibronectin synthesis.^{21,22} Mulhaupt et al⁶ showed that fluoroquinolones cause disintegration of vimentin-containing intermediate filaments, a decrease in pericellular proteoglycans, and an increase in deposits of fibronectin but cautioned that it was not clear whether changes in the extracellular matrix were sufficient or necessary to induce cell death.

One explanation for ciprofloxacin's apoptotic effects may be related to the enzyme topoisomerase II. This enzyme is known to interact with fluoroquinolones and DNA cleavage-enhancing drugs, such as etoposide, through the same interaction domain.²³ When agents that target topoisomerase II bind to this essential enzyme, they convert it into a potent cellular toxin that promotes cell death by introducing breaks in the genetic material.²⁴ Thus, it has been postulated that ciprofloxacin, like other topoisomerase II-interacting agents, acts by transforming topoisomerase II into a DNA replication inhibitor.

Interestingly, two forms of topoisomerase II exist, probably because of a gene-duplication event.²⁵ The gene encoding the α form (*TOP2A*) is located on chromosome 17 and that for the β form (*TOP2B*) is on chromosome 3. Topoisomerase II α is highly expressed in certain types of tumors, making them more susceptible to topoisomerase II α -interacting agents. Ciprofloxacin-treated chondrosarcoma cultures and tissue samples show changes in cartilage matrix composition, clumped glycogen, dilation of the endoplasmic reticulum, numerous abnormal lysosomes containing degenerated products, and decreased proteoglycan deposits surrounding the tumor cells.⁶ Treatment of chondrosarcoma cells and tissue specimens with ciprofloxacin blocks cell proliferation, with immunohistochemical evidence of apoptosis.⁶ In comparison, ciprofloxacin-treated normal chondrocytes show a decrease in cell proliferation but no apoptosis

or effect of the drug on the expression of extracellular matrix proteins. Finally, the in vitro growth of other non-cartilaginous malignant tumors, such as osteosarcoma and liposarcoma, is unaffected by ciprofloxacin.⁶

Ciprofloxacin's effect on gene expression

Ciprofloxacin's antitumor activity in chondrosarcoma is possibly mediated by topoisomerase II. However, one study found that ciprofloxacin shows little ability to stimulate DNA cleavage and acts instead as a competitive inhibitor of other topoisomerase-targeting antineoplastic drugs.²³ Discovering this, we directed our attention to other possible explanations for its effect. We decided to investigate gene expression in both normal cartilage and chondrosarcoma cells exposed to ciprofloxacin in vitro, focusing on the differential expression of genes known to be involved in apoptosis, cell growth, and cell-cycle regulation.

We found that ciprofloxacin decreased the growth of chondrosarcoma cells in culture. The genes differentially expressed and involved in apoptosis, cell growth, and cell-cycle regulation included *DDX5*, *MYST2*, *ISGF3*, *APC*, *RPL3*, *EIF4G2*, and *ERH* (Table 1).

DDX5, also known as DEAD box polypeptide 5, codes for a protein that is implicated in a number of cellular processes involving alteration of the secondary structure of RNA, including translation initiation, nuclear and mitochondrial splicing, and ribosome assembly. *MYST2* codes for a protein involved in the inhibition of active demethylation of DNA and silences transcription. *ISGF3* codes for interferon-stimulated transcription factor 3 gamma. This gene product plays a role in transcription regulation. *APC* is a gene that encodes a tumor suppressor protein involved in cell-cycle regulation. Defects in this gene cause familial adenomatous polyposis, an autosomal dominant premalignant disease that usually progresses to malignancy.

Ribosomal protein L3 (*RPL3*), also known as *TARBP-B*, encodes a ribosomal protein and plays a role in RNA binding and protein biosynthesis. The gene product of *EIF4G2*, also known as eukaryotic translation initiation factor 4 gamma 2, functions as a general repressor of translation by forming translationally inactive complexes. This gene has also been shown to be involved in cell-cycle arrest and cell death. Although few data on *ERH* (enhancer of rudimentary homolog) exist, this gene is thought to play a role in cell-cycle regulation.

It is not possible to determine from our work whether the differential expression of these genes is a direct result of ciprofloxacin exposure, leading to apoptosis and decreased growth or it is just a side effect or random difference between our treated and untreated cells. Further studies are needed to verify the role of these genes in the ciprofloxacin-induced effects seen in vitro.

Study limitations

The primary weakness of our study is the low patient number, which precluded statistical analysis. The lack of a control group is another limitation. Each patient served as his own control, and tumor growth rates were compared before and after treatment. Previous unpublished studies performed at our institution showed

TABLE 1
Functions of genes that were differentially expressed and involved in cell-cycle regulation, cell growth, or apoptosis

Gene	Function
<i>DDX5</i>	Affects translation initiation
<i>MYST2</i>	Affects DNA replication
<i>ISGF3</i>	Implicated in transcription regulation
<i>APC</i>	Negative regulation of the cell cycle
<i>RPL3</i>	Ribosomal binding of RNA and protein synthesis
<i>EIF4G2</i>	Repressor of translation
<i>ERH</i>	Cell-cycle regulation

that ciprofloxacin and paclitaxel have a synergistic effect on the growth of human chondrosarcoma cells in vitro. Thus, our clinical study included both drugs in the treatment regimen, which limited our ability to determine the in vivo effects of each drug alone. In addition, the use of MRI and CT to measure tumor size introduces a small amount of error due to intra-observer and interobserver error, aside from the inherent limitations of these imaging techniques.

Our in vitro study had its own limitations. Gene expression profiling using cRNA does not necessarily correlate with protein synthesis. However, it does offer a way to obtain an initial estimate of gene expression, which was the purpose of our investigation.

Conclusion

Our study further elucidates the potential role of ciprofloxacin and paclitaxel in the treatment of chondrosarcoma. Although no patients had a complete or partial response, preliminary results look promising. The combination of ciprofloxacin and paclitaxel decreased tumor growth rates in several recurrent or metastatic chondrosarcomas but did not decrease growth rates in all lesions. The regimen was well tolerated. Overall, ciprofloxacin and paclitaxel appear to slow clinical tumor growth and provide some disease stability. Changes in fluorodeoxyglucose (FDG) avidity on positron emission tomography (PET) scan were not utilized in this study but may be a useful parameter for future research. Our current gene expression study, as well as our previous in vitro studies, correlate with our clinical findings of decreased tumor growth. Further studies are required to determine the statistical significance of these findings and the exact mechanism by which this treatment affects chondrosarcoma growth. Further research may also provide even better methods for treating chondrosarcoma recurrences and metastases.

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