Chemotherapy-Related Arthropathy

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ABSTRACT. ***Objective.*** To examine the characteristics of chemotherapy-related arthropathy in patients with cancer.
Methods. Eighteen patients developed joint symptoms after receiving chemotherapy. We reviewed their charts to obtain information on demographics, underlying tumor, chemotherapeutic agents, rheumatologic symptoms, and laboratory findings. Each patient was interviewed by telephone about his or her current joint symptoms.
Results. Patients comprised 14 women and 4 men with mean age 53.9 ± 10.6 years. Five patients had breast cancer, 3 had advanced gastric cancer, 3 had lung cancer, 2 each had colon and cervical cancer, and 1 each had lymphoma, glioblastoma, and bladder cancer. The most commonly used drugs were 5-fluorouracil, cyclophosphamide, and cisplatin. Joint symptoms usually began 6 months after the first session of chemotherapy. Patients had an average of 8 tender joints and 6 hours of morning stiffness. Five patients were positive for antinuclear antibody and 3 for rheumatoid factor. Nonsteroidal antiinflammatory drugs and disease modifying antirheumatic drugs (DMARD) were prescribed. Five patients did not show improvement and were also given low dose oral corticosteroids. Followup was available for 15 patients: 14 showed favorable responses characterized by a significant decrease (more than 50%) in morning stiffness, pain, and tender joint counts after a mean of 3 months' treatment. Nine patients had complete resolution of symptoms and stopped all medications.
Conclusion. Chemotherapy-related arthropathy is not rare and the prognosis is fairly good with early treatment using DMARD and corticosteroids. (J Rheumatol 2006;33:1364–8)

Key Indexing Terms:
CANCER CHEMOTHERAPY ARTHRITIS TREATMENT

Rheumatic manifestations associated with malignancy have been well documented, although many associations are based only on a small number of case reports[1-5]. These manifestations may be due to direct invasion of the joints and muscles by the tumor, paraneoplastic syndrome induced by a distant tumor via humoral factors, altered immune surveillance that causes both rheumatic and neoplastic disease, and adverse reactions to anticancer therapy.

Several rheumatic manifestations may develop in patients after receiving chemotherapy for treatment of malignancy. There are reports on development of rheumatoid arthritis (RA), Reiter's syndrome, and vasculitis in patients undergoing immunotherapy or radiotherapy, and of exacerbation of RA after chemotherapy[6-9]. Additionally, postchemotherapy rheumatism has been described in patients treated for breast cancer, ovarian cancer, and non-Hodgkin's lymphoma[10-15]. The phenomenon has been described as a temporary, noninflammatory, self-limiting, migratory, musculoskeletal pain syndrome. Characteristically, stiffness, arthralgia, and arthritis involving both large and small upper and lower extremity joints develop within a few months after completion of combination chemotherapy. These symptoms can occur without evidence of metastatic disease and without positive laboratory and radiologic findings that are indicative of rheumatic disease.

Although chemotherapy-related joint symptoms have been related to treatment of cancer, evidence has been limited because most reports involve single or multiple cases with similar disease, such as breast cancer. Therefore, we examined the occurrence and prognosis of chemotherapy-related arthropathy in patients with a variety of cancers over a short period.

MATERIALS AND METHODS

Our study comprised 18 patients who were referred from January 2002 to July 2003 to the arthritis center at Ajou University Hospital because of newly developed or aggravated preexisting joint symptoms while receiving chemotherapy. The predominant complaint was stiffness upon arising after periods of inactivity, and myalgia and arthralgia during adjuvant or palliative systemic chemotherapy and also after completion of chemotherapy.

We reviewed their charts to obtain information on demographics, underlying tumor, dates of initiation and discontinuation of systemic chemotherapy, chemotherapeutic regimen, and other treatments such as radiotherapy and/or surgery. The 18 patients had no evidence of metastatic cancer at the time of evaluation. Clinical examination was performed by a rheumatologist (CHS). We asked about duration of morning stiffness, and their subjective pain intensity was evaluated using a 10 cm visual analog scale (VAS) for pain. Joint tenderness and swelling were assessed in 44 joints and pain on passive motion was evaluated in hip joints. Arthritis was verified based on evidence of joint inflammation such as tenderness and swelling; otherwise arthralgia was considered. We documented positivity for rheumatoid factor (RF) and antinuclear antibody (ANA), and inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at the initial visit. Patients had radiographs of their hands and feet. The patients were treated according to the clinical judgment of the rheumatologist rather than by an

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algorithm. Because several reports about chemotherapy-related joint symptoms showed that treatment with only nonsteroidal antiinflammatory drugs (NSAID) was not adequate for controlling joint symptoms, our patients were initially managed with NSAID and disease-modifying antirheumatic drugs (DMARD) if there was evidence of joint inflammation. Low dose corticosteroids were added if joint symptoms did not improve after 2 weeks. Medication was tapered and eventually discontinued if the joint symptoms disappeared. Finally, each patient was interviewed by telephone for 10-20 minutes after giving their verbal consent. They were questioned about the duration, resolution, and change in severity of their joint symptoms, particularly in relation to the administration of medications.

RESULTS

Patients included 14 women and 4 men; the mean age was 53.9 ± 10.6 years (range: 27-72 yrs) and the mean followup duration was 21.5 ± 22.3 weeks (range: 4-64 wks). Patients had various cancers; 5 had breast cancer, 3 had advanced gastric cancer (AGC), 3 had lung cancer, 2 each had colon or cervical cancer, and 1 each had lymphoma, glioblastoma, and bladder cancer (Table 1). Ten patients received radiation therapy during and after combination chemotherapy. Twelve patients had undergone surgical removal of their tumor. Three patients received only palliative chemotherapy. Diverse chemotherapeutic agents were used for the adjuvant and palliative chemotherapy. The most commonly used drug was 5-fluorouracil (FU). Cyclophosphamide, cisplatin, mitomycin-C, and paclitaxel were also commonly prescribed. All drugs were administered intravenously (IV) with a mean treatment cycle of 4 weeks. For antiemetics, all patients received 5-HT_3 antagonist and metoclopramide IV on each day of their chemotherapy, and 11 patients were given IV steroids.

Sixteen patients had no joint symptoms prior to administration of chemotherapy, and 2 experienced a significant exacerbation of previous symptoms as well as additional new symptoms: Patient 8 had arthralgia of the right fingers and developed morning stiffness and pain in both knees and shoulders; Patient 16 had arthralgia of all fingers for 10 years and the joint symptoms were aggravated and spread to wrists, feet, and temporomandibular joints. Joint symptoms usually began 6 ± 3 months (range: 1-14 mos) after the first session of chemotherapy (Table 2). In 10 patients symptoms began within 5 months after the last session of chemotherapy, in 8 patients during chemotherapy, and in 4 patients within 4 months after the first session of chemotherapy. They complained of 6 hours of morning stiffness (range: 0-24 h) and had, on average, 8 tender joints (range: 2-14). The commonly involved joints were fingers, toes, shoulders, and knees (Table 3). Fourteen patients showed a symmetrical distribution. Four patients complained of joint pain without evidence of joint inflammation such as tenderness and swelling; these patients had arthralgia without arthritis. Fourteen patients had arthritis: 11 cases of polyarthritis and 3 cases of pauciarthritis. Most patients showed nearly normal inflammatory markers: mean ESR 21.6 ± 14.4 mm/h (range: 0-47) and mean CRP 0.27 ± 0.4 mg/dl (range: 0.02-1.18). Five patients were positive for ANA and 2 for RF. For the 5 patients who had a positive ANA, 2 (Patients 1 and 18) discontinued medication because their

Table 1. Treatment of patients with chemotherapy-related arthropathy.

Patient	Gender	Age	Tumor Site/ Diagnosis	Adjuvant Chemotherapy (n courses)	Other Treatment
1	F	50	AGC	5FU, MMC(4), 5FU, cisplatin (6), 5FU, irinotecan (6)	OP
2	M	61	Bladder	Unknown	OP
3	F	50	Breast	FAC (4), paclitaxel (4)	OP + RTx
4	F	43	Breast	FMC (3), tamoxifen maintenance	OP + RTx
5	F	65	AGC	5FU, MMC (4)	OP
6	F	43	Cervix	Cisplatin (4), paclitaxel, cisplatin (2)	OP + RTx
7	F	27	AGC	5FU, cisplatin (6), 5FU, irinotecan (6)	OP + RTx
8	F	52	Breast	FAC (6)	OP + RTx
9	M	58	Colon	5FU, campto (6), 5FU, eloxatin (4)	OP
10	M	61	Lung	Carboplastin, ifosfamide (4), irinotecan (5)	OP + RTx
11	F	49	Lymphoma	Cyclophosphamide, doxorubicin, vincristine, PL (6)	No
12	F	51	Colon	5-FU (6)	OP + RTx
13	F	52	Breast	FMC (6)	OP
14	F	72	Lung	Paclitaxel, carboplatin (2), gemcitabin, vinorelbine (4), irresa	No
15	F	57	Breast	FAC (4), paclitaxel (4)	RTx
16	M	69	Glioblastoma	Unknown	RTx
17	F	60	Cervix	5-FU, cisplatin (2)	RTx
18	F	51	Lung	Gemcitabin, cisplatin (4), gefitinid	No

AGC: advanced gastric cancer; 5-FU: 5-fluorouracil; MMC: mitomycin-C; FAC: 5FU, doxorubicin, cyclophosphamide; FMC: 5FU, mitomycin-C, cyclophosphamide; MTX: methotrexate; PL: prednisolone; OP: surgery; RTx: radiation therapy.

Table 2. Characteristics of patients with chemotherapy-related arthropathy. Some patients stopped their medications voluntarily due to lack of pain; in other cases, the physician stopped the medication because of complete resolution of joint symptoms. Time to improvement was defined as time from symptom onset to more than 50% improvement of symptoms (months).

Patient	Symptom Onset, mo (after n courses CTx)	Positive Serology	Medication (Specific Drug)	Time to Improvement	Result
1	2 (6)	ANA	NSAID, DMARD (S)	6	Stopped medication voluntarily, complete resolution of joint symptoms
2	1 (6)	RF	NSAID, DMARD (S)	—	Stopped medication voluntarily, lost to followup
3	2 (4)	—	NSAID, DMARD (H)	4	Stopped medication voluntarily, complete resolution of joint symptoms
4	2 (3)	RF	NSAID, DMARD (H, S) PDS	5	Stopped medication voluntarily, recurrent joint pain
5	1 (4)	—	NSAID, DMARD (B)	6	Partial resolution of joint symptoms (> 50%)
6	1 (1)	—	NSAID, DMARD (H)	1	Partial resolution of joint symptoms (> 50%)
7	1 (5)	—	NSAID, DMARD (B,S) PDS	2	Complete resolution of joint symptoms, physician stopped medication, developed bone metastasis
8	2 (6)	—	NSAID, DMARD (H)	2	Complete resolution of joint symptoms, physician stopped medication
9	1 (3)	—	NSAID, PDS	1	Partial resolution of joint symptoms (> 50%)
10	5 (5)	—	NSAID	—	Stopped medication voluntarily, lost to followup
11	1 (6)	—	NSAID, PDS, DMARD (H)	1	Complete resolution of joint symptoms, physician stopped medication
12	1 (3)	—	NSAID, DMARD (B,M), PDS	2	Partial resolution of joint symptoms (> 50%)
13	1 (6)	—	NSAID, DMARD (H)	1	Stopped medication voluntarily, complete resolution of joint symptoms
14	1 (3)	—	NSAID, DMARD (B)	8	Stopped medication voluntarily, complete resolution of joint symptoms
15	1 (4)	ANA	NSAID, analgesics	5	Partial resolution of joint symptoms (> 50%)
16	1 (1)	ANA	NSAID, DMARD (H)	—	Died
17	4 (2)	ANA	NSAID, DMARD (H)	—	Continuing medication
18	2 (4)	ANA	NSAID, DMARD (H)	1	Complete resolution of joint symptoms, physician stopped medication

CTx: chemotherapy; ANA: antinuclear antibody; RF: rheumatoid factor; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease modifying antirheumatic drug; H: hydroxychloroquine sulfate; B: bucillamine; S: sulfasalazine; M: methotrexate; PDS: oral corticosteroid.

symptoms were completely resolved and one (Patient 15) had only partial resolution of symptoms after receiving NSAID. Of the 2 patients with RF, one (Patient 4), who showed only partial resolution of symptoms with NSAID and DMARD, had complete resolution of symptoms after receiving additional low dose oral corticosteroids, but her symptoms returned with a greater severity after she voluntarily stopped the corticosteroids. Five patients satisfied the American College of Rheumatology (ACR) criteria for classification of RA: 2 patients stopped medication due to complete resolution of joint symptoms, one showed partial resolution of joint symptoms, one died, and one was lost to followup.

Among the 18 patients, 15 completed the study and 3 were lost to followup. One patient died and 2 were lost due to their continuous pain; both tried complementary and alternative medicine. All patients initially received NSAID and/or DMARD. Five patients found no improvement with these medications, and were given additional low dose oral corticosteroids. Of the 15 patients who were followed, 14 showed favorable responses characterized by a significant decrease (more than 50%) in duration of morning stiffness, VAS for pain, and tender and swollen joint counts at a mean period of 3 months (range: 1-6 mos) after treatment, and one (Patient 17) showed no improvement. Among those whose symptoms did improve, 9 had complete resolution of joint symptoms, and their medication was either stopped by us or voluntarily by the patients; 5 had decreased joint symptoms but continued to receive medication.

DISCUSSION

Various musculoskeletal manifestations can develop in a patient after administration of chemotherapy for treatment of malignancy. We identified 18 patients who, after starting chemotherapy, developed arthritis or arthralgia within a relatively short period, about 19 months. Among these, 16 patients had no symptoms prior to administration of chemotherapy, and 2 patients had significant exacerbation of previous symptoms and developed new symptoms. Half the

Table 3. Distribution of the symptomatic joints in the patients with chemotherapy-related arthropathy.

Patient	Arthralgia	Tender Joints/Pain on Motion	Swollen Joints	Morning Siffness, h
1	Ankles, toes, back	0	0	0
2	Toes, ankles, knees, elbows, shoulders	Both 2nd-4th MTP, ankles, knees, elbows, shoulders	0	0
3	Fingers	Lt hip	0	2
4	Fingers and toes, back	Both 4th PIP, 2nd-4th MTP, elbows, TMJ, Rt 5th MCP, Rt 2nd, 3rd PIP, Lt ankle	0	24
5	Knees, back	0	0	3
6	Wrists, ankles, elbows, shoulders	Both 4th MTP, ankles, shoulders, Rt elbow, Lt wrist	0	0
7	Fingers, toes, knees, shoulders	Both 1st–5th PIP, ankles, wrists and TMJ, Lt 2nd–4th MCP, Lt elbow, Lt knee, Rt hip	0	24
8	Knees, shoulders	Knees, shoulders	0	1
9	Rt fingers	Rt 4th MCP, Rt 3rd, 4th PIP	0	5
10	Shoulders, neck	0	0	0
11	Fingers, ankles, neck, back	Both 2nd–4th PIP ad 2nd–4th MCP, ankles	0	1
12	Fingers	Both 1st MCP, 1st–5th PIP	0	24
13	Fingers, knees, shoulders, neck	0	0	0
14	Ankles and shoulders	Both 3rd–5th PIP, SCJ, Rt 3th MCP, Rt wrist, Rt ankle, Rt elbow, Rt TMJ	0	1
15	Knees, back	Rt 3rd PIP, Rt knee, Rt elbow, Rt TMJ, Lt shoulder	0	0
16	Rt fingers, both toes	Both 2nd, 3rd MCP, 2nd, 3rd PIP, 2nd–4th MTP, wrists, TMJ	Both 2nd, 3rd MCP, 2nd, 3rd PIP, 2nd–4th MTP, wrists	1
17	Rt knee, both shoulders	Knees, elbows, shoulders	0	0
18	Both fingers, Lt toes and ankle	Both 4th, 5th PIP, Lt 3rd MCP, Lt 1st–3rd PIP, Lt 3rd to 5th MTP	0	24

MTP: metatarsophalangeal joint; MCP: metacarpophalangeal joint; PIP: interphalangeal joint; TMJ: temporomandibular joint; SCJ: sternoclavicular joint; Rt: right; Lt: left.

patients developed joint symptoms while receving chemotherapy and the remainder developed symptoms within 5 months after the last dose of chemotherapy. Joint symptoms were well controlled by NSAID and DMARD with/without corticosteroids in most patients, but not all.

Musculoskeletal symptoms after administration of chemotherapy were first reported as postchemotherapy rheumatism by Loprinzi, *et al*[10]. They described 8 patients who developed joint symptoms 1-2 months after receiving adjuvant chemotherapy for breast cancer with a regimen of cyclophosphamide, methotrexate, and 5-FU. Treatment with NSAID was ineffective, but symptoms abated in most patients within a year. Others have reported similar cases for patients with breast cancer, ovarian cancer, and lymphoma[11-15]. There are several differences between the patients who had postchemotherapy rheumatism and our patients.

First, our patients had more heterogeneous malignancies and chemotherapeutic regimens. Although breast cancer was the most common tumor in our cohort, gastric cancer, lung cancer, colon cancer, cervical cancer, lymphoma, glioblastoma, and bladder cancer were also found. Various chemotherapeutic agents were involved such as 5-FU, cyclophosphamide, cisplatin, doxorubicin, mitomycin-C, and paclitaxel among others. These findings suggest that musculoskeletal symptoms may develop independent of type of cancer or chemotherapeutic regimen.

Second, the patients with postchemotherapy rheumatism developed arthralgia in a short period after finishing chemotherapy. However, half of our patients developed joint symptoms while receiving chemotherapy and 4 reported symptoms within 4 months after the first session of chemotherapy. This temporal relationship strongly suggested that chemotherapy can induce joint symptoms.

Third, our patients showed definite evidence of joint inflammation such as tenderness and swelling. The description of postchemotherapy rheumatism in the previous study was vague about joint inflammation, and some patients had fibromyalgia-like symptoms. We designated the joint symptoms seen in our patients chemotherapy-related arthropathy, in contrast to postchemotherapy rheumatism, because there was definite evidence of joint inflammation. For chemotherapy-related arthropathy, the clinical manifestations were similar to RA: morning stiffness, polyarthritis, frequent involvement of fingers and toes, and symmetric distribution. However, there were some differences from RA: only 2 patients were positive for RF, only 5 patients satisfied the ACR criteria for RA, and inflammation markers were normal in most of our patients.

The fourth difference between our results and those of

Loprinzi is the response to treatment and the prognosis. No patient with postchemotherapy rheumatism responded to NSAID and responses to corticosteroid therapy were variable; most symptoms resolved spontaneously within 1 year. In our cohort, however, 14 patients among the 15 patients available for followup responded to NSAID and DMARD with or without concomitant corticosteroid therapy. The response was rapid, as early as 1 month taking medication, and the response time ranged up to 8 months. Nine patients were completely free of joint symptoms and 5 patients still reported arthralgia despite receiving medication. Another 4 patients showed no improvement with medication; 2 patients were lost to followup due to the continuous joint symptoms, and 1 patient died. It seems likely that complete resolution of pain in most of our patients was a result of initial administration of DMARD. We used a variety of DMARD: hydroxychloroquine, sulfasalazine, bucillamine, and methotrexate. For patients who showed an unsatisfactory initial response, the addition of corticosteroids resulted in improved joint symptoms. An important matter for the management of chemotherapy-related arthropathy is early detection and early administration of NSAID and DMARD with/without corticosteroids.

Pathophysiologic mechanisms of chemotherapy-related arthropathy remain uncertain. There is a suggestion that combination chemotherapy may disturb the immune system so profoundly as to break the self-tolerance of a patient, resulting in the production of autoantibodies and musculoskeletal manifestations[16]. This idea is supported by a report that gonadal ablation by chemotherapy can result in thymic hyperplasia and altered thymic function that leads to autoimmunity[17]. In our patients, 5 were positive for ANA and 2 were positive for RF. Development of rheumatic symptoms in patients treated with tamoxifen has been described[18]. Several observations suggest that tamoxifen may induce or exacerbate arthritis through its antiestrogen effect[15]. It is possible that chemotherapy and tamoxifen may induce gonadal atrophy, and this results in T cell activation and autoimmune manifestations.

Chemotherapy-related arthropathy is not a rare event, and the physician's awareness of this syndrome is important as it may limit the need for extensive investigation to exclude recurrent cancer or other rheumatologic disease. The most important point is that early diagnosis and early treatment lead to a better prognosis.

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