## Nonsteroidal Antiinflammatory Drugs (NSAID) Versus NSAID with Hydroxychloroquine in Treatment of Chemotherapy-related Arthropathy: Open-label Multicenter Pilot Study

*To the Editor:*

Various musculoskeletal manifestations can develop in a patient receiving chemotherapy for malignancy[1,2,3,4,5,6]. We previously examined the occurrence and prognosis of chemotherapy-related arthropathy (CRA) in 18 patients with a variety of cancers with favorable responses after a mean of 3 months' treatment with nonsteroidal antiinflammatory drugs (NSAID) and disease-modifying antirheumatic drugs (DMARD)[7]. However, that study was limited by the small number of enrolled patients and its retrospective design. Therefore, on the basis of our previous report, a multicenter randomized open-label pilot study was designed to evaluate whether adding hydroxychloroquine (HCQ) to NSAID modifies disease activity in CRA.

Our study was conducted in accord with the ethical principles of the Declaration of Helsinki and was approved by the institutional review boards of the hospitals involved. We obtained written informed consent from all participants. We registered our trial in the database of the Clinical Research Information Service (http://ncrc.cdc.go.kr/cris: KCT0000160) as a randomized clinical trial (RCT).

The open-labeled RCT was carried out at 7 tertiary hospitals from April 2007 to June 2011. The patients were randomized 1:1 to receive NSAID alone or NSAID with HCQ for 3 months. Patients were examined at baseline and after 3 months of treatment. If the patients did not show improvement of symptoms during the followup period, they could be given low-dose oral corticosteroids, acetaminophen, or tramadol.

Patients included 65 women (81.3%) and 15 men; the mean age was 51.4 ± 9.2 years (range 31–82 yrs). Breast cancer was the most common cancer (42 patients, 51.2%). Various other cancers were diagnosed, including lymphoma, advanced gastric cancer, lung cancer, and cervical cancer. The most commonly used drugs were cyclophosphamide, adriamycin, and 5-fluorouracil. Nineteen of 42 patients with breast cancer received aromatase inhibitor after chemotherapy. Joint symptoms usually began 8.5 ± 13.3 months after the first session of chemotherapy. Fifty-nine patients had joint symptoms during the chemotherapy. Among 80 patients, 46 were withdrawn during the screening and followup period. Of the 34 patients who were followed up for 3 months, 20 patients received NSAID only (NSAID-alone) and 14 patients received NSAID with HCQ (NSAID-HCQ).

*Table 1.* Clinical features of chemotherapy-related arthropathy. Data are mean ± SD unless otherwise indicated; data were analyzed by Mann-Whitney U test. Categorical values were compared by chi-square test.

| Features | NSAID-Alone Group | NSAID-HCQ Group | p |
|---|---|---|---|
| Total patients, n (%) | 20 (100) | 14 (100) | |
| Sex, F/M | 17/3 | 13/1 | 0.627 |
| Age, years | 46.6 ± 7.5 | 48.1 ± 7.2 | 0.538 |
| Surgery, n (%) | 16 (80) | 10 (71.4) | 0.689 |
| Radiation therapy, n (%) | 11 (55) | 8 (57.1) | 1.0 |
| Extraarticular symptoms, n (%) | 2 (10) | 2 (14.3) | 1.0 |
| Morning stiffness, min | 461.1 ± 634.7 | 455 ± 649.8 | 0.799 |
| Pain VAS, mm | 5.1 ± 2.2 | 5.3 ± 2 | 0.928 |
| Tender joint counts | 5.9 ± 4.7 | 6.1 ± 6.5 | 0.666 |
| Swollen joint counts | 1.4 ± 2.6 | 3.1 ± 4.5 | 0.569 |
| ESR, mm/hr | 13.2 ± 9.3 | 30.9 ± 23.4 | 0.003 |
| CRP, mg/dl | 0.14 ± 0.13 | 0.3 ± 0.35 | 0.419 |
| Hemoglobin, g/dl | 12.4 ± 0.8 | 12.8 ± 0.7 | 0.138 |
| Leukocyte, $\mu$l | 4568 ± 1911 | 4535 ± 1455 | 0.522 |
| Positive RF or ACPA, n (%) | 2 (10) | 0 (0) | 0.501 |
| Positive ANA, n (%) | 2 (10) | 2 (14.3) | 1.0 |

For RF, ACPA, and ANA-positive patients, the diagnosis of rheumatoid arthritis or systemic lupus erythematosus could be excluded according to the American College of Rheumatology criteria[8,9]. NSAID: nonsteroidal antiinflammatory drugs; HCQ: hydroxychloroquine; RF: rheumatoid factor; ANA: antinuclear antibody; ACPA: anticitrullinated protein antibodies; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

There were no significant differences in age or sex between the NSAID-alone group and the NSAID-HCQ group (Table 1). The erythrocyte sedimentation rate (ESR) was higher in the NSAID-HCQ group than in the NSAID-alone group at baseline (p = 0.003). After 3 months, statistically significant reductions of tender joint count of 44 joints and pain visual analog scale (VAS) were observed in both the NSAID-alone group and the NSAID-HCQ group. However, a statistically significant reduction of ESR was observed only in the NSAID-HCQ group (Table 2). We compared improvement of disease activity after 3 months' treatment. The ESR was much improved in the NSAID-HCQ group compared to the NSAID-alone group (p = 0.004).

Clinical characteristics of the study are similar to our previous report[7]. Patients in our study also had heterogeneous malignancies and chemotherapeutic regimens. Most patients had definite evidence of joint inflammation, with an average of 6 tender joints and 2 swollen joints. In addition, the joint symptoms of patients in our study developed 8.5 ± 13.3 months after the first session of chemotherapy. Therefore, we could confirm clinical features of CRA. When we evaluated clinical features of patients with breast cancer according to medication with aromatase inhibitor, there were no differences in the clinical features between patients who received aromatase inhibitor and those who did not (data not shown).

The data on treatment for postchemotherapy rheumatism have been very limited and retrospective. The difference between the treatment response found by Loprinzi, *et al*[1] and our previous report was also evident. In the study by Loprinzi, *et al*, no patient with postchemotherapy rheumatism responded to NSAID, and responses to corticosteroid therapy were variable[1]. In our study, based on our previous reports[7], we evaluated whether adding HCQ to NSAID modifies disease activity in CRA, because the patients had definite evidence of joint inflammation. After 3 months' treatment, the tender joint count of 44 joints and pain VAS were significantly improved in both groups. However, the ESR was significantly improved only in the NSAID-HCQ group. These results suggest that NSAID are effective for CRA and that HCQ may be used for patients with CRA who have elevated ESR.

Our study was limited in that the sample size was small, and the ESR of the NSAID-HCQ group was higher than that of the NSAID-alone group at baseline. Therefore, we could not exactly compare efficacy of the drugs between the 2 groups. Additionally, about half the patients were lost to followup during this trial. They did not follow up in the rheumatology outpatient clinic although they regularly visited an oncologist. We thought that was because patients with CRA were more concerned about their cancer than about their arthritic symptoms.

NSAID may be effective in controlling joint symptoms in patients with CRA. HCQ, which has the potential to modulate inflammation[10], may be beneficial for patients with CRA who have elevated ESR.

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*Table 2*. Followup data of patients with chemotherapy-related arthropathy treated with nonsteroidal antiinflammatory drugs alone (NSAID-alone) and those treated with NSAID with hydroxychloroquine (HCQ). Data were analyzed by Wilcoxon signed-rank test; categorical values were compared by chi-square test.

| | NSAID-alone | | | NSAID-HCQ | | |
|---|---|---|---|---|---|---|
| | Initial | After 3 Months | p | Initial | After 3 Months | p |
| Total patients, n (%) | 20 (100) | | | 14 (100) | | |
| Morning stiffness, min | 461.1 ± 634.7 | 99.7 ± 290.1 | 0.24 | 455 ± 649.8 | 53.9 ± 85.6 | 0.094 |
| Pain VAS, mm | 5.1 ± 2.2 | 2.7 ± 2.3 | 0.004 | 5.3 ± 2 | 2.2 ± 1.7 | < 0.001 |
| Tender joint counts | 5.9 ± 4.7 | 2.0 ± 2.8 | 0.003 | 6.1 ± 6.5 | 0.8 ± 1.8 | 0.002 |
| Swollen joint counts | 1.4 ± 2.6 | 0.7 ± 1.6 | 0.496 | 3.1 ± 4.5 | 0.1 ± 2.9 | 0.106 |
| ESR, mm/hr | 13.2 ± 9.3 | 8.8 ± 8.5 | 0.132 | 30.9 = 23.4 | 12 ± 13.4 | 0.009 |
| CRP, mg/dl | 0.14 ± 0.13 | 0.09 ± 0.12 | 0.116 | 0.3 ± 0.35 | 0.07 ± 0.05 | 0.112 |
| Hemoglobin, g/dl | 12.4 ± 0.8 | 12.5 ± 1.1 | 0.74 | 12.8 ± 0.7 | 13.1 ± 0.7 | 0.154 |
| Leukocyte, $\mu$l | 4568 ± 1911 | 5335 ± 1759 | 0.08 | 4535 ± 1455 | 4630 ± 1155 | 0.841 |
| Steroid added, n (%) | | 9 (45) | | | 5 (35.7) | |
| Other medication added, n (%) | | 8 (40) | | | 6 (42.9) | |

VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

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