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Anti-Lymphoma Effect of Naproxen and Indomethacin in a Patient With Relapsed Diffuse Large B-Cell Lymphoma

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A 77-year-old man with relapsed non-Hodgkin's lymphoma, diffuse large B-cell type, was treated with naproxen, a nonsteroidal anti-inflammatory drug (NSAID), for paraneoplastic fever.

A dramatic disappearance of not only the fever but also generalized lymphadenopathy was observed. Naproxen was continued, and he maintained remission for 10 months. When relapse of lymphoma occurred in spite of continuous naproxen administration, indomethacin, another type of NSAID, was tried. Surprisingly, rapid regression of lymphoma occurred again and was maintained for almost 1 year. These results indicate that NSAIDs are effective in some patients with non-Hodgkin's lymphoma. Am. J. Hematol. 66:220–223, 2001. © 2001 Wiley-Liss, Inc.

Key words: non-Hodgkin's lymphoma; naproxen; indomethacin; nonsteroidal anti-inflammatory drugs

INTRODUCTION

Naproxen and indomethacin, both of which are nonsteroidal anti-inflammatory drugs (NSAIDs), have been used as antipyretic agents in febrile patients with many types of malignancies [1–3]. Recently, several investigators have shown that NSAIDs have anti-neoplastic effects in clinical and in vitro studies. Clinically, aspirin has been shown to reduce the risk of colorectal cancer [4,5]. In vitro experiments, the induction of apoptosis of several colon carcinoma cells, myeloid cells, and lymphoid cells by NSAIDs has been demonstrated [6,7]. In this report, we present for the first time that NSAIDs such as naproxen and indomethacin induced long-term remission in a patient with relapsed diffuse large-cell lymphoma.

CASE REPORT

A 77-year-old man presented with weight loss and generalized lymphadenopathy in July 1990.

An incisional biopsy of the cervical lymph node was performed, and the diagnosis of malignant lymphoma, diffuse large B-cell was made. He was treated with a half dose of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy and reached complete remission in August 1991. In total, 17 courses of CHOP were carried out. In October 1992, generalized lymphadenopathy was appeared again and a re-biopsy of the inguinal lymph node was performed. Relapse of diffuse large-cell lymphoma was confirmed by histology and the presence of abnormal karyotype [47XY, -13, -15, +3, +t(1q;15q), +t(3p;13q)]. Because a slight fever not related with infection was also recognized, 300 mg per day of naproxen was started on November 12, 1993 (Fig. 1). Surprisingly, in addition to the resolution of fever, generalized lymphadenopathy also decreased after the administration of naproxen. In January 1994, he reached complete remission, accompanying normalization of the serum lactic dehydrogenases level. Thereafter, naproxen was continued without additional chemotherapy. In October 1993, generalized lymphadenopathy and high-grade fever appeared again. Naproxen was stopped, and indomethacin, another type of NSAID, was administered

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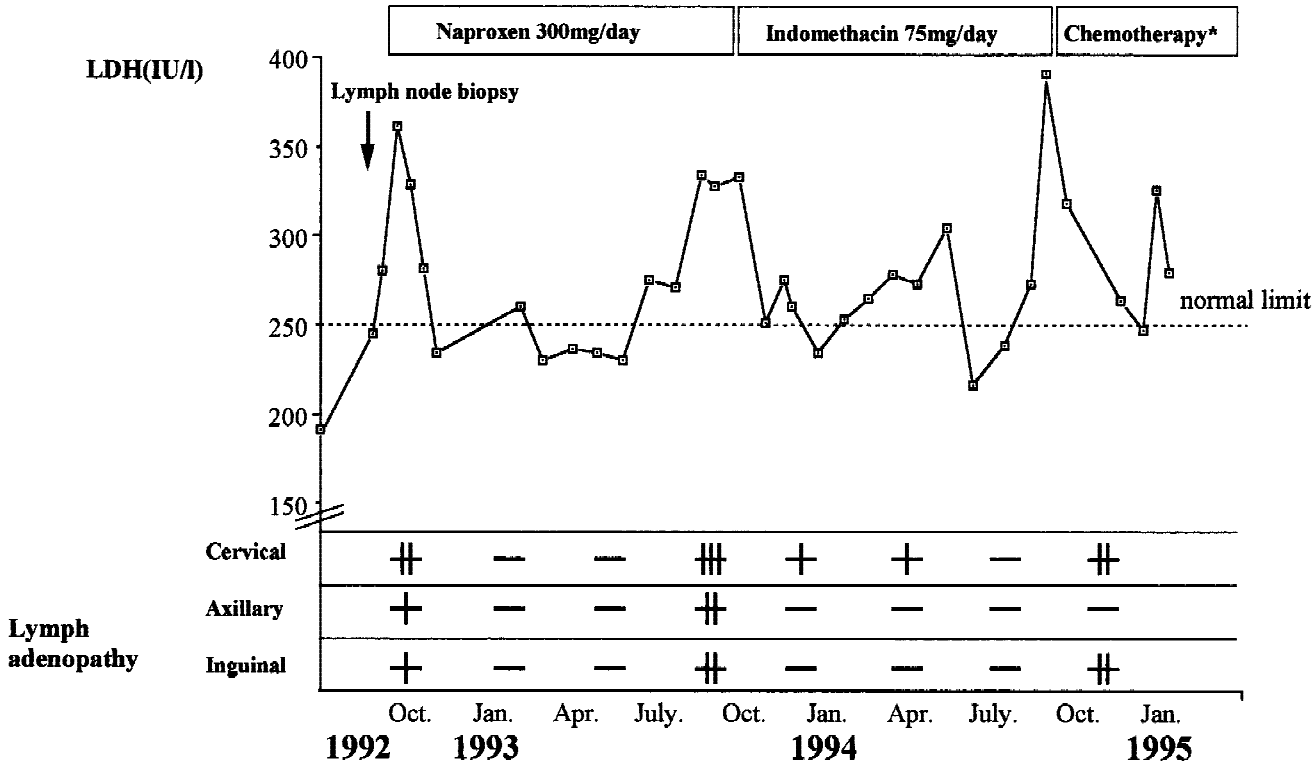

Fig. 1. Clinical course. "Chemotherapy*" refers to chemotherapy containing behenoyl aranofuranosyl cytosine (BHAC) and mitoxantrone.

at 75 mg per day. More than 50% regression of lymph node swelling was obtained again and remained unchanged for one year.

In November 1995, enlargement of lymph nodes occurred again. Indomethacin was discontinued, and he received several courses of chemotherapy containing behenoyl arabinofuranosyl cytosine (BHAC) and mitoxantrone. Complete remission was achieved, and he was still alive without any signs or symptoms of relapse in January 2000, 10 years after presentation.

DISCUSSION

We presented a case of relapsed non-Hodgkin's lymphoma in which naproxen and indomethacin revealed anti-lymphoma effects. There are a few rare reports concerning the spontaneous remission of lymphoma [8,9]. However, in this case, a dramatic regression of lymphoma occurred at the time in which naproxen was started. Furthermore, when naproxen was changed to indomethacin because of recurrence, a rapid regression of lymphadenopathy occurred again. From this clinical course, we believe that NSAIDs such as naproxen and indomethacin have anti-lymphoma effects in some patients with non-Hodgkin's lymphoma.

Recently, data have been accumulating that support the anti-neoplastic effects of NSAIDs both in clinical and experimental studies. Clinically, several investigators reported a 30–50% decrease in the relative risk of colorectal cancer in persons who are continuous users of aspirin or other NSAIDs [4,5]. In animal models, NSAIDs mediating the suppression of several neoplastic cells including colon carcinoma, fibrosarcoma, mast cell tumor, lung carcinoma, and bladder carcinoma have been reported [10].In hematological malignancies, the induction of apoptosis of B-cell chronic lymphocytic leukemia cells and myeloid leukemia cells by aspirin and salicylate has also been reported [6,7].

The reasons why NSAIDs exert anti-lymphoma effects are unclear. However, it is possible to speculate several mechanisms such as inhibition of cyclooxygenase (COX), suppression of cytokine production, modulation of cell cycles, and induction of apoptosis which might be responsible for the anti-lymphoma effects of NSAIDs [6,7,10–17].

Aspirin and other NSAIDs directly inhibit COX, a key enzyme in the production of prostaglandins, prostacyclins, and thromboxanes. There are two COX isoenzymes, COX-1 and COX-2, which differ in their expression regulation and tissue distribution and could be selectively inhibited. COX-2 is highly expressed in human colorectal cancers and polyps of mouse familial polyposis (FAP) models. Inactivation of COX-2 gene in FAP model mice dramatically reduces the number and size of polyps [10].

Because COX-2 is known to be expressed in some types of B-cell lymphoma [11], it is possible that lymphoma suppressive effects of NSAIDs might be related to COX-2 inhibition.

Another possible mechanism is NSAID-mediated inhibition of cytokine production. It has recently been shown that NSAIDs such as aspirin and sodium salicylate inhibit the activity of IκB kinase-β;.As a result, NF-κB is inactivated, and consequently the production of various cytokines including interleukin-6 (IL-6) was suppressed [12,13]. It has also been reported that several NSAIDs, including indomethacin, ibuprofen, and fenoprofen, have peroxisome proliferator-activated receptor-γ;(PPAR-γ) agonist activity and then inhibit the production of monocyte inflammatory cytokines such as IL-6, IL-1β, and TNF-α;[14]. In our patient, the disappearance of lymphadenopathy, fatigue, and tumor fever occurred simultaneously after the administration of NSAIDs. It is well known that tumor fever is related to cytokines such as IL-6, IL-1β, IFN, and TNF produced by host macrophages in response to the tumor or by the tumor itself. It has also been reported that IL-6 acts as autocrine growth factor in several B cell lymphoid malignancies [15]. Taken together, in the present case, it is speculated that NSAIDs inhibit the proliferation of lymphoma cells by suppressing the production of cytokines which are responsible for lymphoma growth in an autocrine or paracrine manner.

Schiff et al. have demonstrated that NSAIDs could modify the cell cycle phase distribution [16]. Aspirin, indomethacin, naproxen, and piroxicam, which represent four distinct chemical classes of NSAIDs, inhibit the proliferation, alter the morphologic appearance, and modify cell cycle phase distribution of HT-29, a colon adenocarcinoma cell line. They increased the proportion of cells in the G0/G1 phase and reduced the proportion in the S phase of the cell cycle. Aspirin and indomethacin also reduced G2/M phase cells but naproxen did not. From these data, one can deduce that NSAIDs inhibit lymphoma cells by cell cycle modification.

It has recently been shown that NSAIDs inhibit angiogenesis, the formation of new capillary blood vessels, which is essential for growth and metastasis of solid tumors. The mechanism of inhibition of angiogenesis involves the inhibition of mitogen-activated protein (MAP) kinase (ERK2) activity [17]. It has also been reported that NSAIDs modulate apoptosis signal pathways, such as caspase, subsequent cleavage of poly (ADP-ribose) polymerase (PARP) and gelsolin [6,7]. These mechanisms may also be related to the effects of NSAIDs on lymphoma cells.

Of particular interest was the observation that indomethacin was effective for lymphoma which had become refractory to naproxen. This clinical data indicate that the mechanism of NSAIDs action on lymphoma cells is complicated and different according to each NSAID. Therefore, it is clinically useful to try another kind of NSAID if patients are refractory or becoming resistant to one drug.

In the literature, tumor regression treated by NSAIDs has been reported in some patients with Hodgkin's disease following treatment with phenylbutazone [18]; however, there are no reports in non-Hodgkin's lymphoma. Given our experience, the single administration of naproxen or indomethacin maintained good condition in a patient for two years. NSAIDs may be alternative agents for patients with relapsed non-Hodgkin's lymphoma, especially for elderly patients. Further studies are needed to clarify the role of NSAIDs in lymphoma.

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