Neoplastic Fever Responds to the Treatment of an Adequate Dose of Naproxen

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Twenty-one patients with neoplastic fever due to malignancy were treated with naproxen. A prompt and complete lysis of fever was obtained in 20 patients within 12 hours when an adequate dose of naproxen was given, and a sustained normal temperature was maintained in all responding patients while receiving naproxen except for one in whom a low grade fever recurred. Lysis of fever usually was followed by excessive sweating and subjective symptomatic improvement. However, when naproxen was discontinued in ten patients, febrile state to the pretreatment level recurred in seven patients within three days. This observation suggests naproxen has a definite and effective antipyretic activity against neoplastic fever although it may recur as the drug is discontinued. Naproxen may be a useful adjunctive agent in patients with neoplastic fever for a short-term symptomatic relief. ***J Clin Oncol 3:552–558. © 1985 by American Society of Clinical Oncology.***

FEVER is a very common problem occurring in patients with cancer during the course of the disease and is usually attributed to infection related to immunocompromised state, from either cancer itself or chemotherapy. However, neoplastic fever also is not uncommon in patients with cancer, and the incidence was estimated to be approximately 5% in studies of the 1960s.[1,2] Despite careful clinical investigation, fever in certain patients with cancer often cannot be ascribed to coexistent infection or other known causes. The major association of neoplastic fever has been observed with Hodgkin's disease, myxoma, hypernephroma, and osteogenic sarcoma, but it has also been seen in various other cancers.[3–6] Clinical observation suggests advanced cancer with metastases tends to produce neoplastic fever more often than cancer in an earlier stage.[2] Although cancer itself is a major problem requiring careful attention and management, neoplastic fever is also a vexing problem because of its high morbidity and the necessity to differentiate from debilitating infectious fever.

Recently we have reported that naproxen is a useful agent in the differential diagnosis of fever of undetermined origin in patients with cancer.[7] According to the study, neoplastic fever usually was completely lysed by naproxen treatment within 24 hours of the initiation of the drug, and symptomatic improvement related to the abatement of neoplastic fever was apparent. In contrast, no patient with infectious fever showed any significant response to naproxen. Standard antipyretic drugs are generally ineffective in reducing neoplastic fever, and much less in suppressing it entirely. In the present study, we have further evaluated the value of naproxen in the treatment of neoplastic fever.

MATERIALS AND METHODS

The patients with the diagnosis of neoplastic fever treated at the Good Samaritan Hospital and Health Center, Dayton, Ohio, between November 1982 and June 1984 were entered for this evaluation and analysis. All patients had well-established diagnoses of cancer, and most of them were receiving intensive chemotherapy during hospitalization. The patients were not preselected, but those meeting the following diagnostic criteria were included for the study. The criteria for neoplastic fever were as previously described[7]: (1) temperature at least once >101 °F, (2) duration of fever over one week, (3) no evidence of infection on careful physical examination, (4) negative results of adequate blood and urine cultures, (5) absence of pneumonia on chest roentgenography, (6) normal findings in spinal fluid in patients who underwent spinal puncture, and (7) lack of evidence of drug fever. In addition, another criteria, (8) lack of evidence of infection on continuous evaluation during hospitalization, is added. Prior to the initiation of naproxen, other antipyretics were discontinued if possible, or the drugs were proven to not alter the course of fever in a given patient if continued use was necessary for pain management. In all patients, the temperature usually was recorded at least three times per day, and all patients had fever above 100 °F or more within 24 hours before

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the initiation of naproxen. Among 21 patients, 12 patients were initially treated with a course of antibiotics. However, antibiotics were discontinued at the time of the initiation of naproxen. Nine patients were not given antibiotics and treated with naproxen first because neoplastic fever was highly suspected. Even during treatment with either antibiotics or naproxen, the possible cause of fever was continuously sought with careful physical examination and laboratory studies.

The initial naproxen dosage was 250 mg twice a day at 12-hour intervals when patients had fever >100 °F. Adequate treatment was defined as a course of therapy with naproxen 250 mg twice daily for at least three days. If fever response was prompt and complete, the treatment was continued three days or more until clinical improvement of symptoms related to fever. If the patient showed partial or no response in spite of the lack of evidence of infection, naproxen was increased to 375 mg twice per day or up to 1,500 mg per day. Therapeutic responses were defined as follows: complete response—complete lysis of fever to <99 °F within 12 hours after the initiation of naproxen and sustained normal temperature at least three successive days while receiving the drug; partial response—reduction of fever following naproxen of at least 1.5 °F or more but persistent fever >99.4 °F and <101.0 °F while receiving the drug. When the patient became afebrile after naproxen treatment, the drug was continued at least three days, and in some patients it was discontinued after three to seven days of treatment as the patient's symptoms improved. The afebrile course was observed after the withdrawal of naproxen for at least three days.

Because of the relatively short-term treatment with naproxen, stools for occult blood were not systematically examined and its antiplatelet effects not evaluated. However, gastrointestinal symptoms have been closely watched while on naproxen.

RESULTS

Patient Characteristics

In the duration of 20 months total, 21 patients were evaluated adequately and met the criteria of neoplastic fever and were eligible for the analysis of naproxen effect. The clinical features of these patients are summarized in Table 1. There were ten male and 11 female patients. The patients' ages ranged between 15 and 84 years. All patients had the diagnosis of cancer in advanced stage, and 17 were receiving chemotherapy when the febrile state was observed. Four patients had colon cancer with metastases, three had breast cancer with bone metastases, two had multiple myeloma, two had acute myeloblastic leukemia, and two had stomach cancer. One each had Hodgkin's disease, chronic granulocytic leukemia in blastic crisis, lung cancer, malignant melanoma, chronic lymphocytic leukemia, primary hepatoma and biliary tract cancer, and intra-abdominal leiomyomatosis. The known duration of fever was between one week and ten months. All patients had fever at least to 101 °F, and the maximum temperature was as great as 104 °F in two patients. The diagnosis of neoplastic fever was well established or strongly suspected on the basis of the aforementioned criteria after an appropriate evaluation for infection and careful clinical follow-up examination. Ten patients were considered to have an adequate course of antibiotic therapy with a presumptive diagnosis of unidentified infection, but all of them failed to lyse fever on the treatment. All patients had normal urinalysis, and negative blood and urine cultures. Chest roentgenography results were normal in 13 patients. Three patients had mild chronic pulmonary fibrosis in the lung, two had minimal pleural effusion, two had metastatic nodules, and one had minimal atelectasis. Hematologic studies showed anemia in 19 patients and thrombocytopenia in seven. Granulocyte counts were >1,200/μL in 18 patients but severe granulocytopenia of <600/μL was present in three patients. No significant side effects of naproxen were observed in the follow-up of seven days except for one patient who had nausea and vomiting, presumably related to naproxen. The drug was discontinued after five days.

The frequency of neoplastic fever has not been systematically studied in our institution, but it is estimated to be <5% in the total cancer population during the course of their disease.

Naproxen Response

When the diagnosis of neoplastic fever was established or strongly suspected, the patients were started on naproxen 250 mg twice per day. Sixteen patients had complete response with normalization of temperature <99.0 °F within 12 hours. As the patients were continued on naproxen, an afebrile state was sustained with a prompt symptomatic improvement, except for patient No. 16 who, after initial complete lysis, developed a low grade recurrent fever up to 100 °F within one week while on naproxen. As previously observed, lysis of fever was often followed by excessive sweating within the first 12 hours of naproxen treatment.[7] Two patients had a partial response and three patients had no response. Because of incomplete or no response, these five patients were thought to have a hidden or occult infection, and further extensive infectious evaluation including repeated blood and

Table 1. Summary of Clinical Information on Patients With Neoplastic Fever

Patient No.	Age/Sex	Diagnosis	Length of Fever (wk)	Maximum Temperature (°F)	Granulocyte Count (per mm^3)	Antibiotic Treatment Prior to Naproxen	Lysis of Fever to Initial Naproxen	Increase of Naproxen Dose and Response
1	62/M	Multiple myeloma	44+	104.0	21,600		No	375 mg BID Complete lysis
2	64/F	Acute myeloblastic leukemia	2	103.6	294		Complete	
3	59/M	Hodgkin's disease stage IV	3	102.6	3,485		Complete	
4	72/F	Breast cancer with bone metastases	2½	103.2	3,650		Complete	
5	68/F	Breast cancer with bone metastases	1	103.4	4,071	Tobramycin Ampicillin	Complete	
6	71/F	Chronic granulocytic leukemia in blastic crisis	1½	103.6	1,819		Complete	
7	55/F	Colon cancer with liver and lung metastases	3	102.4	2,988		Complete	
8	54/F	Colon cancer with liver metastases	1	102.4	4,408		Complete	
9	41/F	Breast cancer with bone metastases	1	101.4	4,818		Complete	
10	46/F	Stomach cancer with intra-abdominal carcinomatosis	3	103.0	2,542	Cefamandole Penicillin Gentamicin Metronidazole Netilmicin	Complete	
11	59/M	Stomach cancer with liver metastases	2	101.2	4,100	Erythromycin	Partial	375 mg BID Complete lysis
12	51/M	Lung cancer with pleural involvement	2½	103.8	9,102	Tobramycin Ampicillin	Complete	
13	31/M	Malignant melanoma with brain, lung, and skin metastases	1	103.0	176	Tobramycin Ticarcillin	No	250 mg QID Complete lysis
14	71/M	Multiple myeloma	1	101.0	3,726		Complete	
15	79/M	Acute myeloblastic leukemia	1	103.0	23,856	Cefamandole Ticarcillin	Complete	
16	60/M	Chronic lymphocytic leukemia stage IV	4	102.0	540	Tobramycin Nafcillin	Complete	
17	70/F	Colon cancer with liver metastases	2	101.4	8,925	Trimethoprim Sulfamethoxazole	Partial	250 mg TID Complete lysis

Table 1. Summary of Clinical Information on Patients With Neoplastic Fever (Cont'd)

Patient No.	Age/Sex	Diagnosis	Length of Fever (wk)	Maximum Temperature (°F)	Granulocyte Count (per mm^3)	Antibiotic Treatment Prior to Naproxen	Lysis of Fever to Initial Naproxen	Increase of Naproxen Dose and Response
18	15/M	Primary hepatoma with bone metastases	1	102.8	2,460	Methicillin Tobramycin	Complete	
19	74/M	Colon cancer with abdominal carcinomatosis	2	101.0	1,272		Complete	
20	84/F	Bile duct cancer with liver metastases	1	101.4	12,775		Complete	
21	56/F	Intra-abdominal leiomyomatosis	1	104.0	2,808	Tobramycin Ampicillin	No	375 mg QID No lysis

urine cultures as well as physical examination, and a laparotomy in patient No. 21, were performed, but in all five patients no evidence of infection could be uncovered. Patient No. 1 with the diagnosis of multiple myeloma and fever of undetermined origin was studied closely by us from December 1982 to October 1983 without a significant change in febrile pattern. On October 17, the patient was started on a higher dose of naproxen 375 mg twice per day because the diagnosis of neoplastic fever was certain. As seen in Fig 1, a prompt and complete lysis of fever was achieved within 12 hours of naproxen treatment and an afebrile state was sustained while the patient was maintained on naproxen. Because of this experience, four other patients who had either a partial response or no response were started on the higher doses of naproxen. Three patients showed a complete response within 24 hours, however, patient No. 21 failed to show any response (Table 1).

Effect of Naproxen Withdrawal

Minimum duration of naproxen treatment was three days, and in 14 patients the treatment was continued more than seven days. The effect of naproxen withdrawal is summarized in Table 2. In ten patients, when naproxen was discontinued after the treatment, ranging between three days and five weeks, neoplastic fever returned to the pretreatment level in seven patients, usually within 24 hours. Three patients, however, remained afebrile during the three-day observation period. Symptoms related to the febrile state also returned as naproxen was discontinued and fever relapsed. Figure 2 illustrates patient No. 3 with

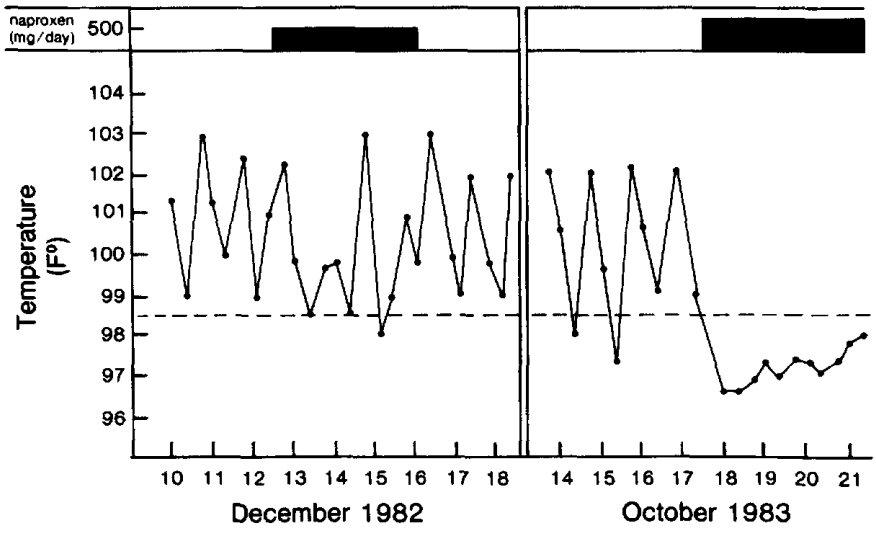

Fig 1. Febrile course of patient No. 1 with neoplastic fever. The patient had a protracted febrile course for ten months. Initially he had no response to naproxen 250 mg twice per day, but complete lysis occurred when the naproxen dose was increased to 375 mg twice per day.

Table 2. Effect of Withdrawal of Naproxen on Neoplastic Fever

Patient No.	Lysis of Fever With Naproxen	Duration of Naproxen Therapy	Relapse of Fever After Withdrawal of Naproxen	Lag Time Before Relapse of Fever
1	Complete	5 wk	No	
2	Complete	3 d	Yes	3 d
3	Complete	3 d	Yes	<24 h
4	Complete	7 d	No	
5	Complete	7 d	No	
7	Complete	7 d	Yes	<24 h
9	Complete	7 d	Yes	<24 h
11	Complete	Over 1 wk	Yes	<24 h
17	Complete	3 wk	Yes	<24 h
19	Complete	5 d	Yes	<24 h

Hodgkin's disease, stage IVB, whose fever responded to naproxen but returned after the withdrawal of the drug. This patient was not taking other antipyretics while receiving naproxen.

DISCUSSION

Neoplastic fever, a recurrent, unexplained fever, related to cancer itself, is one of the most puzzling phenomena of cancer and has made oncology practice ever more difficult in an era of extensive immunosuppressive therapy. Several hypotheses have been proposed to explain neoplastic fever including production of a toxic product by the tumor, tissue necrosis with leukocyte infiltration or release of tissue pyrogen, occult infection or obstruction, abnormalities of liver function with altered conjugation of steroids, or excessive production of heat by tumor cells,[8,9] but with little or no supporting evidence. In bacterial infection, leukocyte or endogenous pyrogen derived from phagocytes in response to stimuli of bacteria is thought to be the mediator for fever production by enhancing prostaglandin E_2 synthesis in the hypothalamus, which is responsible for the upward resetting of the hypothalamic thermostat.[10,11] The mechanism of neoplastic fever is less understood. A pyrogen was demonstrated in urine and tissues of febrile patients with cancer,[12,13] and tumor cells from patients with neoplastic fever were found to produce a pyrogen when incubated in vitro.[8,14] It seems likely that neoplastic fever is a paraneoplastic syndrome mediated by a humoral factor or humoral factors. Another nonsteroidal anti-inflammatory drug, indomethacin, was reported to have an antipyretic effect on neoplastic fever.[15,16] This drug is known to be an inhibitor of cyclo-oxygenase.[17] Cyclo-oxygenase may be an essential enzyme in the production of neoplastic fever through the process of prostaglandin E_2 synthesis mediated by endogenous pyrogen. Endogenous pyrogen released from the human tumor cell lines appears to be similar to endogenous pyrogen from normal human leukocytes.[18] Thus, neoplastic fever, in some instances, is suspected to be due to endogenous pyrogen production by tumor cells.

Fever is a common sign of infection in cancer patients on immunosuppressive therapy. Of 343 patients with malignant diseases, febrile episodes due to infection occurred in 38% of the patients during hospital admission.[2] Fever is also seen after transfusions of blood products, which are often required in patients on immunosuppressive therapy, but usually that subsides within 12 hours after the completion of blood transfusion. It should be emphasized that infectious fever and other noninfectious fever due to drug toxicity, allergic reaction, and adrenal insufficiency must be thoroughly excluded before considering the treatment as neoplastic fever. According to our investigations, neoplastic fever is not an uncommon problem reported in patients who are studied continuously during the course of the disease. This fever is more likely to occur with advanced disease or extensive metastases, especially in lymphoreticular malignancy, a rapidly growing

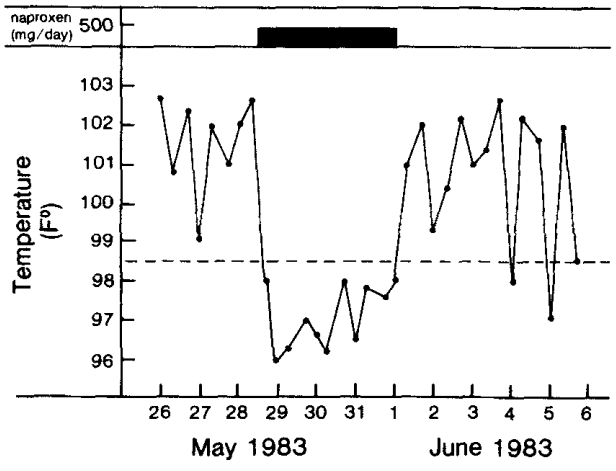

Fig 2. Febrile course of patient No. 3 with neoplastic fever. Fever had a prompt and complete lysis to naproxen, but it recurred within 12 hours to the pretreatment level when the drug was withdrawn.

tumor, and granulocytopenic stage due to the induction chemotherapy of acute leukemia.

Our data indicate that almost every patient with neoplastic fever should respond to naproxen treatment, promptly and completely, if an adequate dose of the drug was administered. Most patients responded to the dose of 250 mg twice per day, although four patients required higher doses. The increased dosage to >375 mg twice per day seems to have had no further advantage in controlling neoplastic fever. Furthermore, the response is sustained only as long as naproxen is continued. One patient did not respond to naproxen, although a laparotomy failed to show any evidence of infection and revealed extensive intra-abdominal carcinomatosis. In this patient, a removal of the bulk of the tumor resulted in some reduction of fever although a low-grade fever persisted postoperatively. When naproxen is discontinued after sustained afebrile state, recurrence of fever to the pretreatment level usually occurs within 24 hours. It is postulated that the mechanism of the action of naproxen may result from either direct interference of the action of fever producing humoral factor or factors, or from the suppression of the synthesis or release of the factor or factors. A modest increase in the dose of naproxen resulted in prompt lysis of fever in patients who failed on 250 mg twice per day. We hypothesize that in those patients initial dose of naproxen was not sufficient enough to interfere with the action or suppress the synthesis or release of humoral factor or factors.

In addition to observed antiplatelet effects of naproxen resulting in prolongation of bleeding time and inhibition of collagen-induced platelet aggregation,[19,20] naproxen, like other nonsteroidal anti-inflammatory drugs, may cause symptoms of gastrointestinal irritation and lead to gastric ulceration and hemorrhage.[21,22] During our initial seven-day observation trial in the treatment of neoplastic fever, we have not observed any obvious gastrointestinal bleeding or significant symptoms of gastric irritation except in one patient. Despite this, the drug must be used with caution, and in our opinion, a long-term treatment of more than two weeks should be discouraged due to the possible development of severe gastritis and/or gastrointestinal bleeding.

In view of the antipyretic effects of naproxen and indomethacin, other nonsteroidal anti-inflammatory drugs such as ibuprofen, fenoprofen, and zomepirac may also have similar antipyretic property on neoplastic fever. Studies are recommended to establish the value of these drugs in the treatment of neoplastic fever. The usefulness of naproxen in the treatment of neoplastic fever is limited by a prompt relapse of fever in most patients when the drug is discontinued. However, a prompt lysis of fever by naproxen may benefit patients as a result of considerable symptomatic improvement. Also, the afebrile state may be sustained in some patients after naproxen is discontinued. Naproxen may prove to be an adjunctive agent to chemotherapy in patients with neoplastic fever for short-term use. It is worth emphasizing that naproxen should be used only after a firm establishment of the diagnosis of neoplastic fever. The premature use of antipyretics in cancer patients receiving chemotherapy is inadequate treatment of infection.

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