Background: The definition of fever is flexible and depends on the clinical context. Fever is frequently observed in patients with cancer.

Methods: Infectious and noninfectious causes of fever in patients with various oncological and hematological malignancies and the usefulness of biomarkers are discussed.

Results: To treat patients in a timely manner and to minimize morbidity and mortality, it is paramount that health care professionals determine the cause of fever. The usefulness of biomarkers in febrile patients with cancer continues to be controversial.

Conclusions: Fever is frequently seen in patients with cancer and can be associated with a variety of infectious and noninfectious causes. The utility of acute-phase reactants, such as erythrocyte sedimentation rate, C-reactive protein, and procalcitonin, along with a nonsteroidal anti-inflammatory drug challenge should be further evaluated as adjunct tools for the workup of fever in patients with cancer.

Introduction

A human's normal body temperature is 37 °C, although this value can change depending on the time of day and the method of measurement used.1 Defining fever is a somewhat arbitrary process because, as the body's temperature is lowered, the rate of sensitivity increases and the rate of specificity decreases.1 Thus, the American College of Critical Care Medicine and the Infectious Diseases Society of America has defined fever as a body temperature of at least 38.3 °C.1,2 For the purposes of this article, we will adhere to this widely accepted definition, although it is worth noting that it is reasonable to use a lower temperature to define fever in patients whose immune systems are compromised.1,2

Fever is frequently seen in patients with cancer and can be associated with a variety of infectious and noninfectious causes. To treat patients in a timely manner and to minimize morbidity and mortality, it is paramount that health care professionals determine the cause of fever. Infections are a principle source of fever in patients with oncological disorders and should be initially considered in both neutropenic and non-neutropenic patients.3 Possible noninfectious causes of fever include alterations of oral mucosa leading to mucositis, certain medication use, blood transfusions, radiation, endocrine disturbances, surgery, and tumor fever.5,6 Moreover, cancer has been reported as the cause of fever in 15% to 20% of patients with fever of unknown origin (FUO).5

Neoplastic Fever

Neoplastic fever, also known as tumor fever, is a diagnosis of exclusion, because no clinical features are consistently present to distinguish it from other causes of fever. Malignancies commonly associated with fever include Hodgkin and non-Hodgkin lymphomas, soft-tissue sarcoma, acute or chronic leukemia, and renal cell carcinoma; however, most types of cancer and benign tumors, such as atrial myxoma, can induce pyrexia.3,5,6 The most common symptoms that occur with neoplastic fever are diaphoresis and rubor but less often include chills/rigor. By contrast, infectious fevers tend to present with warmth, diaphoresis, and chills reflective of peripheral vasodilation. Hypotension and tachycardia commonly accompany systemic infections caused by gram-negative organisms secondary to the production of lipopolysaccharide.5 Pel-Ebstein fever, a stereotypical, noninfectious fever, has been associated with Hodgkin lymphoma and presents in a cyclical pattern of several days of fever followed by afebrile episodes of similar duration, usually 1 to 2 weeks.6 Use of aspirin and acetaminophen allow for defervescence in patients with infectious fever, whereas other nonsteroidal anti-inflammatory drugs (NSAIDs) like naproxen have greater efficacy in neoplastic fever.5

Many attempts have been made to pinpoint and describe the underlying mechanism of tumor fever; however, the full mechanism is still unclear. Pyrogens have been isolated in both the tissue and urine of pa-
patients with cancer presenting with tumor fever. Evidence exists for pyrogen release from tumor cells in vitro. Known primary cytokines released by tumor cells leading to fever production are tumor necrosis factor α, interleukins 1 and 6, and interferon; however, these cytokines are produced during both infection and neoplastic fevers. Pyrogens stimulate the anterior preoptic nuclei of the hypothalamus, leading to the induction of prostaglandin E2 production and an elevated body temperature. The mechanism of release of these substances has been postulated to be from tumor necrosis, bone marrow necrosis, or another unknown mechanism; however, a thorough and exact mechanism for the pathophysiology of tumor fever remains unknown.

A retrospective, observational study by Liaw et al attempted to identify patterns in vital signs in patients with neoplastic fever. Of the 150 patients diagnosed with neoplastic fever, 60% were asymptomatic until fever was recorded in the hospital. The most common daily peak temperatures were between 38 and 38.9 °C in 103 of patients; of those exhibiting intermittent fevers, once-daily spike patterns were seen in 72% of patients, and 93% of patients showed no change in baseline heart rate except during the fever period. A complete and sustained defervescence within 24 hours of administering naproxen was seen in 87%, a partial response in 10%, and a failure to defervesce in 3% of study patients.

The usefulness of naproxen and other NSAIDs to differentiate neoplastic from non-neoplastic fever in patients with cancer was first described in 1984 by Chang and Gross. These authors described a complete and sustained resolution of fever within 24 hours after the administration of naproxen in 15 of 15 patients with neoplastic fever and none of the 5 patients with fever secondary to infection. Several published articles support the use of the naproxen challenge to differentiate neoplastic from non-neoplastic fever in patients with cancer whose previous workup for infection was negative. By contrast, the usefulness of NSAIDs in unselected patients with FUO does not appear to reliably differentiate neoplastic fever from other causes, thus leading health care professionals to exercise caution when using NSAIDs in this setting.

Drug-Induced Fever
Patel and Gallagher define drug-induced fever as a “febrile response coinciding temporally with the administration of a drug in the absence of underlying conditions that can be responsible for the fever.” A unique feature of drug-induced fever is the abatement of pyrexia once the offending agent is withdrawn and has been renally or hepatically cleared. The true incidence of drug-induced fever in patients with cancer is unknown, because this type of fever remains a diagnosis of exclusion, similar to that of tumor fever. One study reported select medication use as the cause of fever in up to 18% of patients with cancer who had noninfectious fevers. It is important for clinicians to consider drug-induced fever in patients with no other identifiable causes for fever in order to prevent the inappropriate and escalating use of antibiotics and use of expensive diagnostic tests. One study found that an episode of drug-induced fever prolongs the length of hospital stay by nearly 9 days, prompting an average of 5 blood culture draws, 3 radiological studies, and use of unnecessary antibiotics.

Drug-induced fever can present in a variety of patterns and degrees of pyrexia. Patients may appear “inappropriately well,” with relative bradycardia and are frequently unaware of the fevers. Other clinical features of drug-induced fever include rash, peripheral eosinophilia, an elevated erythrocyte sedimentation rate, and mild transaminitis. The mechanisms by which drugs can induce fever are divided into 5 categories: altered thermal regulation, mode of administration, pharmacological action, idiosyncrasy, and hypersensitivity. Hypersensitivity is the most common mechanism of drug-induced fever and may be mediated by humoral response.

The onset of drug-induced fever can vary and depends on the specific agent; it can occur at any point in therapy. However, the average time of 7 to 10 days is the median time between the start of the causative therapy and onset of fever. Antimicrobials and antineoplastics have been reported to have the shortest interval between the initiation of therapy and onset of fever. Antineoplastics have a mean onset of 6.0 days compared with 7.8 days in antimicrobials. In addition, no single patient population has consistently been identified to be at an increased risk for drug-induced fever.

Many agents can cause fever, but certain medications are more commonly associated with inducing fever. Antimicrobials, anticonvulsants, bisphosphonates, immunosuppressants, and antineoplastic agents are among the most common agents to induce fevers and are also frequently used in patients with cancer. Bleomycin, chlorambucil, cisplatin, daunorubicin, hydroxyurea, vincristine, and 6-mercaptopurine, among others, can induce fever. Some agents may be more likely to be accompanied by pyrexia than others, so clinicians should be aware of fever as an adverse event of these agents. In patients with hematological malignancies, the use of cladribine has been associated with fever in nearly 70% of cases. Gemcitabine, an agent widely used in the management of solid tumors such as pancreatic, breast, ovarian, and lung cancers, as well as relapsed or refractory lymphomas, induces fever in 20% to 40% of patients. From observational data at our institution (Moffitt Cancer Center, Tampa, FL), on-
set of fever is seen within 24 hours after the infusion of gemcitabine (but most commonly in 6–12 hours).

Antithymocyte globulin is an immunosuppressant used as treatment and prophylaxis of acute organ rejection during transplantation; in the setting of allogeneic hematopoietic stem cell transplantation (HSCT), antithymocyte globulin is also used to prevent graft-vs-host disease, particularly in those with aplastic anemia.\(^{13-15}\) In phase 3 clinical trials, fever was reported in more than 60% of participants and 51% in postmarketing surveillance among patients receiving antithymocyte globulin.\(^{14,15}\) Other commonly used immunosuppressants such as azathioprine, mycophenolate mofetil, and sirolimus may also induce fever after their prolonged use.\(^{10}\)

Monoclonal antibodies were first introduced into practice in the late 1980s when the US Food and Drug Administration approved muromonab for treatment of acute organ rejection.\(^ {16}\) Since then, a variety of monoclonal antibodies exist for use in several nonmalignant and malignant diseases.\(^ {16}\) Alemtuzumab, ipilimumab, ofatumumab, and rituximab are some of the medications in clinical use for the treatment of cancer and graft-vs-host disease.\(^ {16}\) Because monoclonal antibodies are used for the management of hematological and solid-tumor malignancies, clinicians must be aware of the potential adverse events (eg, drug-induced fever) of these agents. Incidence rates of fever vary among monoclonal antibodies, from fewer than 1% in fully human-derived panitumumab to as high as 60% in rituximab, a genetically engineered, chimeric murine/human monoclonal antibody.\(^ {17,18}\)

Supportive care is instrumental in ensuring optimal outcomes in patients with cancer. This includes administration of antiemetics, bisphosphonates, antimicrobials, and colony-stimulating factors for the management of chemotherapy-induced gastrointestinal, infectious, and hematological toxicities. The package inserts for filgrastim and sargramostim report that fever occurs as an adverse event in 12% and 80% of people receiving the drug, respectively, thus making these agents a frequent source of induced fever in patients with cancer.\(^ {19,20}\) We conducted a retrospective chart review of 162 patients at Moffitt Cancer Center with acute myelogenous leukemia who received induction chemotherapy with cytarabine and an anthracycline (7 + 3) followed by filgrastim (n = 28) or sargramostim (n = 134). The data revealed that fever occurred in 0% of patients receiving filgrastim and in 7% of those receiving sargramostim; however, these results were not statistically significant.

Bisphosphonates, including zoledronic acid and pamidronate, are frequently used for the treatment of hypercalcinia and osteolytic bone metastases in patients with malignancy. Data indicate that 21% of patients receiving intravenous administration of zoledronic acid had fever compared with between 15% and 30% of those receiving pamidronate.\(^ {21}\)

Per guidelines from the Infectious Diseases Society of America, fever in the setting of neutropenia warrants use of aggressive antimicrobials in patients at high risk.\(^ {22}\) Choice of therapy depends on multiple factors but traditionally includes cefepime, piperacillin/tazobactam, and meropenem.\(^ {22}\) However, these agents can also be associated with persistence of fever, and they should not be overlooked as the cause of new or ongoing pyrexia in patients with cancer, even in the absence of neutropenia. Beta lactams are used in cancer treatment to manage fever. In 1 study, fever induced by β lactams and piperacillin occurred in 13% and 17% of treated patients, respectively.\(^ {23}\) Eosinophilia was observed in 25% of patients with drug-induced fever secondary to β lactams, and 29% of febrile patients had rash.\(^ {23}\) Case reports of fever secondary to acyclovir, amphotericin B, minocycline, nitrofurantoin, trimethoprim/sulfamethoxazole, and vancomycin use have been also documented in the literature and should be considered in patients with cancer who are receiving these agents.\(^ {10}\)

**Other Noninfectious Causes of Fever**

Similar to patients without malignancies, fever in patients with cancer can be due to venous thromboembolism. Patients with active disease and malignancies are at increased risk for de novo venous thrombosis; the most common include adenocarcinomas of the breast, lung, prostate, alimentary tract, and kidneys. Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, is a manifestation of hypercoagulability in patients with cancer, particularly adenocarcinoma. The phenomenon results in sterile vegetations that typically occur on the mitral or aortic valves of these patients. Other factors predisposing patients with cancer to venous thromboembolism include occlusion by tumor or lymphadenopathy and chemotherapy-induced endothelial injury.\(^ {24}\) Clinicians should be aware of the risk of venous thromboembolism in patients with cancer, thus considering the condition in the differential diagnosis in a febrile patient with cancer.

Guidelines for the evaluation of new-onset fever in adults who are critically ill outline several noninfectious causes of fever that can occur in the oncological population.\(^ {2}\) Fever related to noninfectious, inflammatory states can be associated with any organ (eg, worsening of inflammation after acute myocardial infarction in the setting of Dressler syndrome). Several other etiologies of inflammation associated with noninfectious fever include adrenal insufficiency, gout, intracranial bleeding, pancreatitis, pulmonary infarction, stroke, thyroid storm, and tumor lysis syndrome, among many others not listed here.\(^ {2}\)
A host of symptoms (eg, fever) can be observed in patients with cancer during the neutrophil recovery and after they have undergone cytotoxic chemotherapy. Overproduction of proinflammatory cytokines is the mechanism thought to be responsible for the febrile syndrome. For patients undergoing HSCT, these clinical manifestations can be observed prior to, during, or immediately following neutrophil engraftment (leading to the terms pre- and peri-engraftment fever). The full presentation of these syndromes is beyond the scope of this article, but all of them include fever as part of the presentation with concomitant rash and, oftentimes, pulmonary findings. For clinicians caring for such patients, it is crucial to consider engraftment fever in the differential diagnosis of a febrile patient undergoing HSCT.

Usefulness of Biomarkers

To differentiate between noninfectious and infectious causes of fever, several acute-phase reactants (procalcitonin, C-reactive protein, erythrocyte sedimentation rate) have utility in patients without cancer. The usefulness of biomarkers in febrile patients with cancer is controversial, but some evidence suggests that procalcitonin can discriminate between different causes of fever. Inflammatory conditions, infections, and cancer can induce the synthesis of C-reactive protein and increase the erythrocyte sedimentation rate; thus, their discriminatory ability between neoplastic and infectious fever in patients with cancer is limited.

Procalcitonin is a prohormone of calcitonin and is produced by a variety of tissues in response to inflammation and infections caused by fungi, bacteria, and parasites. In patients with cancer, scant evidence exists regarding the use of procalcitonin levels to discern between infection or acute-phase reaction due to drug use or presence of a tumor. Penel et al analyzed 245 cases of fever in 155 patients with solid-tumor malignancies. Of the 95 patients with infection, 19 had procalcitonin levels above 2 ng/mL; thus, the researchers concluded that procalcitonin failed to discriminate infection. In another study of patients with white blood cell counts below 1000/µL, procalcitonin levels did not rise above 2 ng/mL in those with sepsis or severe sepsis, whereas white blood cell counts above 1000/µL resulted median procalcitonin levels of 4.1 ng/mL and 45.0 ng/mL, respectively. Procalcitonin has several limitations to its use as a marker of sepsis and infection. In the absence of bacterial infection, elevated levels of procalcitonin can occur during extremely high times of stress or during systemic inflammation without an infectious etiology. For example, the stress of labor, acute graft-vs-host disease, and several types of immunotherapy, among many other causative conditions, may cause false-positive procalcitonin levels. Additional data are needed to assess the role and cutoff values of procalcitonin in febrile neutropenic and non-neutropenic patients with cancer. Moreover, serial procalcitonin levels should be obtained to establish a trend, because baseline levels may be elevated in patients with cancer.

Conclusions

Fever is common in patients with cancer and is associated with several types of infectious and noninfectious causes. Although infection remains the main etiology of fever in patients with cancer, noninfectious causes should also be considered following the negative results of a thorough workup for infection. Neoplastic fever, drug-induced fever, and venous thromboembolism are all important causes of fever in patients with hematological and solid-tumor malignancies. The usefulness of acute-phase reactants, such as erythrocyte sedimentation rate, C-reactive protein, and procalcitonin, along with a nonsteroidal anti-inflammatory drug challenge should be further evaluated as adjunct tools for the workup of fever in patients with cancer.

References


