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Diagnosis, Pathology, Treatment, and Nursing Considerations for Cancer of Unknown Primary

B.D., a 55-year-old woman with increasing abdominal pain and bloating accompanied by a 23-pound weight loss, was found to have multiple liver lesions during a computed tomography (CT) scan on March 21. A liver needle core biopsy conducted April 3 showed the adenocarcinoma and the following pathology report: Immunoreactive to cytokeratin, 19; cytokeratin, 7; monoclonal antibody epithelial-related antigen, 31; and anti-cytokeratin, 5.2. Also immunoreactive to estrogen receptor. Gross cystic disease fluid protein, chromogranin, cytokeratin 20, hepatocyte antigen, caudal-related homeobox 2, mesothelin, and thyroid transcription factor-1 were negative.

This immunohistochemical profile and histologic findings are nonspecific but suggest a breast or possibly a gynecologic primary. Less likely is a tumor of pancreatobiliary origin. The human epidermal growth factor receptor 2 (HER2) protein expression was 3+ (normal: 0–3+). Tumor marker carcinoembryonic antigen (CEA) was greatly elevated at 21,828 ng/ml (normal: 0–4 ng/ml). Positron-emission test (PET) scan was negative for other areas of disease. A standardized diagnostic approach was followed. No specific tissue type that may help with the development of a treatment regimen. Biopsy of a mass often results in a histologic diagnosis, possibly identifying a specific tissue type that may help with the development of a treatment regimen.

Overview

Oncology nurses often see cancers that are unusual or rare. Diagnosis and tumor identification are possible but, unfortunately, some patients develop a cancer of unknown primary (CUP). CUP often is metastatic at diagnosis and, because of the rarity of the disease, presents a challenge for oncology nurses educating their patients. Symptoms of metastatic cancers, such as lung or breast, can be taught, but CUP presents with no known primary and often multiple symptoms of metastatic disease (pain or weight loss). This unknown can be scary for patients and nurses. This article will review CUP, diagnosis, pathology, treatment, and nursing considerations.

Epidemiology

CUP accounts for about 2%–3% of all cancer diagnoses (Hainsworth & Greco, 2008b). An estimated 31,490 cases with 45,090 deaths occurred in 2008 (American Cancer Society, 2008)—the difference between figures is from lack of specificity in recording the underlying cause of death on certificates (Tan, Amar, & Perry, 2007). The average age at diagnosis was about 60, with more men being affected than women (Cancer.net, 2008). CUP is defined as “histologically confirmed metastases in the absence of a specific primary tumor despite a standardized diagnostic approach” (Pentheroudakis, Biasoulis, & Pavlidis, 2007, p. 418). Workup of this metastatic disease often will not identify a primary site. Biopsy of a mass often results in a histologic diagnosis, possibly identifying a specific tissue type that may help with the development of a treatment regimen. On autopsy, common identifiable sites of primary tumor are hepatobiliary tree, lung, and pancreas (Hainsworth & Greco, 2008b).

Because many patients have metastatic disease at presentation, such as lung, bone, liver and lymph nodes, they often are very ill, have poor performance status, and can decline rapidly (Hainsworth & Greco, 2008b). Nonspecific symptoms may include weight loss, fatigue, and anorexia (Pentheroudakis et al., 2007; Tan et al., 2007). Favorable prognostic factors include tumor in lymph nodes, soft tissue, less sites of metastatic disease, female, good performance status, normal lactate dehydrogenase, normal albumin, and normal
lymphocyte count (Hainsworth & Greco, 2008b). Patients with adenocarcinoma of unknown primary (AUP) have a median survival of only 4–6 months for unfavorable prognostic factors and 10–16 months with favorable prognostic factors (Pentheroudakis et al.). Other reports show median survival rates from 11 weeks to 11 months (Tan et al.).

Workup of Cancer of Unknown Primary

Once a biopsy has been performed, pathology will attempt to identify tissue of origin such as an adenocarcinoma. Cancers often will stain or look like their tissue of origin. With CUP, the cell type is sometimes the only identification to guide treatment. Histologically, CUP can fall into five different groups: adenocarcinomas (70%), poorly differentiated carcinoma (15%–20%), poorly differentiated neuroplasm (5%), squamous cell carcinoma (5%), and neuroendocrine (5%) (Hainsworth & Greco, 2008b).

A workup is conducted after the initial biopsy to identify the primary tumor. Patients should receive a complete history and physical, routine complete blood count, metabolic panels, urinalysis, and stool for guiac (Hainsworth & Greco, 2008b). Chest x-ray or chest CT, abdominal or pelvic CT, and PET scans may be indicated. Women should have both a pelvic examination and mammography. Men should have a prostate examination along with prostate-specific antigen levels (Hainsworth & Greco, 2008b). Other testing may be indicated if any scans return positive results, such as biopsy of a breast lesion or colonoscopy if positive for stool guiac.

Additional testing on the tissue may be warranted in an attempt to identify a primary. Pentheroudakis et al. (2007) evaluated numerous CUP specimens in an attempt to determine if certain similar abnormalities can be identified and found chromosomal abnormalities of the short arm of chromosome 1 in 12 of 13 CUP samples. Staining for c-Myc (96%), ras (92%), and HER2 (65%) proteins were found in 26 CUP cases. Endothelial growth factor receptor was found in 40%. Vascular endothelial growth factor was found in 83% of 81 CUP samples. However, Pentheroudakis et al. recognized that the different protein expressions failed to show any prognostic significance for patient survival (see Figure 1). Additional study may allow these protein expressions to be treated with their counterpart chemotherapy drugs (HER2/neu positive with herceptin or lapatinib). In B.D.’s case, the tumor was estrogen and HER2/neu positive.

Tumor markers can be drawn but often do not help with diagnosis. Potential markers to use include CEA, CA 27-29, CA 19-9, CA 15-3, CA-125, and AFP (Tan et al., 2007). One or more of these markers may be elevated in patients with CUP, so their use as diagnostic tool is limited. B.D. had an extremely elevated CEA. Response to therapy may be followed by monitoring these markers if previously elevated.

Treatment

For patients with AUP, sites of disease often include liver, lungs, lymph nodes, and bones. On postmortem examination, primary sites found most often are of the lung, gastrointestinal tract, and pancreas (Hainsworth & Greco, 2008a). National Comprehensive Cancer Network ([NCCN], 2009) guidelines include treatment of AUP with agents such as paclitaxel and carboplatinum; paclitaxel, carboplatinum, and etoposide; docetaxel and carboplatinum; gemcitabine and cisplatinum; and gemcitabine and docetaxel. Carboplatinum was used with B.D. and she also received trastuzumab because she was HER2/neu positive.

Squamous cell carcinoma of unknown primary may present as adenopathy; sites of adenopathy may assist with determination of primary site. Inguinal adenopathy may denote a primary of genital or anorectal area while upper and cervical adenopathy may be carcinoma of head and neck (Hainsworth & Greco, 2008b). Other adenopathy may indicate metastatic lung cancer. Squamous cell CUP can be treated with paclitaxel, cisplatinum, and 5-FU or docetaxel, cisplatinum, and 5-FU (NCCN, 2009).

Neuroendocrine tumors of unknown primary present as metastatic carcinoid or islet cell tumors, small cell carcinoma (possibly of bronchogenic origin), or poorly differentiated neuroendocrine carcinoma (Hainsworth & Greco, 2008b). The tumors often are highly aggressive with multiple metastatic sites. Treatment of neuroendocrine tumors of unknown primary with chemotherapy can involve paclitaxel, carboplatinum, and etoposide; cisplatinum and etoposide; temzolomide; and temozolomide and thalidomide (NCCN, 2009). Patients who present with single solitary CUP lesions require surgery as treatment; post-surgery radiation and/or chemotherapy also may be indicated.

Greco et al. (2002) studied 113 patients with CUP treated with gemcitabine, carboplatinum, and paclitaxel and found that 28 patients (25%) had major objective response to treatment. Grade 3/4 toxicities of leukopenia, thrombocytopenia, and fatigue were the major treatment-related effects. Newer agents also have been studied in patients with CUP. Hainsworth et al. (2007) examined 51 patients who had been treated previously or who had no prior treatment. Patients received bevacizumab 10 mg/kg every two weeks along with 150 mg erlotinib orally daily. Five of the patients (10%) had partial responses with 29 (61%) having stable disease. Major toxicities included fatigue, rash, diarrhea, proteinuria, and stomatitis.

Nursing Considerations

Patients with CUP create a special challenge for oncology nurses. Patients often present very ill with vague symptomology, poor performance status, and
an undefined diagnosis. The initial biopsy may have already been done in the oncology office. From there, the oncologist will order appropriate testing such as scans, colonoscopies, additional biopsies, lab work, or mammograms in an effort to determine the primary site. The tests can put a tremendous strain on the patient and family. The oncology nurse can be instrumental in teaching the patient about the tests ordered along with ensuring that the patient understands instructions for each test (such as contrasts for CT scans). The oncology nurse also can help set up a calendar for the patient because many different appointments will be needed. Nurses also can ensure that the patient has a return appointment for general follow-up (to be sure testing is moving forward) or when results are back for additional discussion. Nurses also can advocate for the patient to have the tests done in the most timely and efficient manner.

Nurses also will have a role once a decision is made to start treatment. Whether radiation, surgery, or chemotherapy is undertaken, the oncology nurse can help prepare the patient for the expected side effects through education. This first visit should come as a separate visit after the initial treatment plan has been presented so that patients are not overwhelmed with information. Written and verbal information should be given to the patient with time allocated for questions. Patients should be encouraged to write down questions which arise at home. Nurses should encourage patients to have one person along with them to listen to the information being given. That person can help the patient disseminate information to the family and friends.

Symptom management can become extremely important in this group of patients. They may present in a somewhat debilitated physical state. Oncology nurses will have to help triage symptoms, teach about symptom management, and instruct on when to call the healthcare team. Patients need to know that access to their healthcare team is not only limited to normal business hours; they need guidance on when to call and access to the appropriate phone numbers. Nurses can assist by triaging patients and phone calls or by having patients seen by an advanced practice nurse, if available, to evaluate severity of symptoms. This can allow for frequent assessment of the patient to ensure continuity of care. Issues such as pain management, nausea control, lymphedema management, weight loss, anorexia, constipation, and abnormal laboratory findings (i.e., elevated bilirubin levels) often are symptoms patients with CUP may present with or develop from treatment.

Because of the poor prognosis of CUP, patients and family may have difficulty accepting the diagnosis and illness. The speed at which patients progress often is astounding and leaves little room for patients and family to prepare. As seen with B.D., less than two months passed from diagnosis to death. Palliative care and symptom management should be a focus of care from the time of diagnosis. Helping patients and families move from active treatment to hospice care may need to occur in a very short time period. In some cases, patients present with such poor performance status that active treatment may never occur, so referral to hospice may become the only option. Oncology nurses can help patients and families make that transition when and if the time arrives. Working with the family after the patient’s death may include reviewing findings from an autopsy, if obtained, to help them understand what happened.

Conclusion

CUP is uncommon and oncology nurses may not see many patients with CUP but often will remember the difficulties the patients presented. The CUP diagnosis brings with it an unknown component that oncology nurses can help with by being supportive, teaching about symptom management, and helping patients and their families on this difficult cancer trajectory. Oncology nurses will be challenged to take care of patients with this unusual diagnosis.

The author takes full responsibility for the content of the article. The author did not receive honoraria for this work. No financial relationships relevant to the content of this article have been disclosed by the author or editorial staff.

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