Carcinoma of Unknown Primary Origin

Gauri R. Varadhachary

ABSTRACT

Carcinoma of unknown primary origin (CUP) is a heterogeneous group of cancers defined by the presence of metastatic disease with no identified primary tumor at presentation. Identifying patients with prognostically favorable disease is important, since they may derive substantial benefit, including prolonged survival, from directed treatment. In CUP cases, a focused search for the primary tumor is recommended. Whether CUP is a distinct molecular genotype-phenotype relative to metastases of known cancers is unknown. However, use of a robust immunohistochemical panel and emerging molecular data may permit development of a tailored treatment algorithm for CUP patients that will include appropriate use of targeted agents.

Gastrointest Cancer Res 1:229–235.

G.R. Varadhachary, MD: Department of Gastrointestinal Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX

Submitted November 7, 2006
Accepted February 2, 2007

Carcinoma of unknown primary origin (CUP) is a diverse group of cancers that is defined by the presence of metastatic disease with no identified primary tumor at initial presentation.[1] CUP has been reported to comprise approximately 2% to 5% of all cancer cases. With the availability of sophisticated imaging techniques and targeted therapies in the treatment of cancer, the extent of workup in CUP remains a challenge and should be based on the clinical presentation, pathology, and the patient's ability to tolerate therapy.

The criteria for CUP include a biopsy-proven malignancy for which the anatomic origin is unknown after a medical history has been obtained, a detailed physical examination has been performed, and liver and kidney function tests, blood tests, chest radiography, abdomen and pelvis computed tomography (CT), and mammography or a prostate-specific antigen (PSA) test have been performed.[2] Most investigators also prefer to exclude lymphoma, metastatic melanoma, and metastatic sarcoma, because stage- and histologic type-based treatments are available for these diseases. As discussed below, most CUP cases are limited to epithelial and undifferentiated cancers.

BIOLOGIC CHARACTERISTICS OF CUP

In CUP, the primary tumor may remain diminutive and thus escape clinical detection or it may disappear after seeding the metastasis. It is also possible that it is contained or has been eliminated by the body's defenses. CUP may be a malignant development that results in increased metastasis or survival relative to the primary tumor. However, whether CUP metastases are genetically and phenotypically unique remains to be determined.

The roles of chromosomal and molecular abnormalities in CUP have been evaluated in several studies, but to date no CUP characteristics have been identified that are unique relative to those of metastases from known primary tumors. Abnormalities in chromosomes 1 and 12 and other complex abnormalities have been found.[3] Aneuploidy has been identified in 70% of CUP patients with metastatic adenocarcinoma or undifferentiated carcinoma. The overexpression of several genes, including Ras (92%), Bcl-2 (40%), Her-2 (11%), and p53 (26%–53%) has been found in CUP, but the presence of such abnormalities seems to have no effect on response to therapy or survival.[4-6]

It has been theorized that in CUP, the angiogenic incompetence of the primary tumor leads to marked apoptosis and cell turnover, resulting in a cancer that acquires a metastatic phenotype; however, this theory cannot be clinically tested.[7] Karavasilis and colleagues[8] evaluated 81 CUP tissue samples for tissue expression of CD34, vascular endothelial growth factor (VEGF), and thrombospondin-1. They found VEGF expression in all cases and strong expression in 83% of cases. The extent of angiogenesis in CUP relative to that in metastases from known primaries has also been evaluated, but no consistent findings have emerged.[9]

CLINICOPATHOLOGIC DIAGNOSIS OF CUP

A complete family and personal medical history along with physical examination are essential in CUP cases, with attention to previous surgeries and lesions. A detailed pathologic examination of biopsied tissue is also mandatory and typically consists of hematoxylin-and-eosin staining and immunohistochemical tests. Electron microscopy is rarely used at our institution, though it may occasionally help with treatment decisions.[10]

Light Microscopy Evaluation

A fine-needle aspiration biopsy is usually sufficient in CUP cases, though a core

Address correspondence to: Gauri R. Varadhachary, MD, Associate Professor, Department of Gastrointestinal Medical Oncology, Unit 426, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4009. Phone: (713) 792-2828; Fax: (713) 745-1163; E-mail: gvaradha@mdanderson.org.

biopsy may be performed if feasible. Biopsied tissue should first be evaluated by light microscopy with hematoxylin-and-eosin staining. On light microscopy, most CUP cancers are identified as adenocarcinoma (~60%) or poorly differentiated adenocarcinoma or undifferentiated carcinoma or neoplasm (~30%–35%); the remaining lesions are squamous cell carcinoma (~5%) or neuroendocrine cancers (~2%). CUP also may occasionally present as mixed tumors, such as adenosquamous carcinoma, adenocarcinoma with neuroendocrine components, or sarcomatoid carcinoma.

Immunohistochemical Tests

Immunohistochemical markers, usually peroxidase-labeled antibodies against specific tumor antigens, are helpful in determining the tumor lineage.[10] PSA and thyroglobulin (to detect prostate and thyroid cancers, respectively) are the most specific of the currently available markers; however, prostate and thyroid cancers rarely present as CUP. Also, no test is 100% specific, including the PSA test, which can be positive in patients with salivary gland carcinoma.[11] Communication between the pathologist and the clinician is essential to a correct diagnosis and cannot be replaced by a battery of stains.

There are 20 known subtypes of cytokeratin (CK) intermediate filaments, all of which have different molecular weights and levels of expression in different cell types and cancers. Monoclonal antibodies to specific CK subtypes have been used to help classify tumors according to their site of origin; the most commonly used CK stains in CUP adenocarcinoma cases are CK 7 and 20. CK 7 is expressed in upper gastrointestinal tract tumors, cholangiocarcinoma, and pancreas, lung, ovary, endometrium, and breast cancers, whereas CK 20 is normally expressed in the lower gastrointestinal epithelium, urothelium, and Merkel cells.[12] The CK 20+/CK 7- phenotype suggests a colon primary tumor; 75%–95% of colon tumors show this pattern of staining. CK 20-/CK 7+ is found in several cancer types, such as lung, breast, ovarian, and endometrial cancers. Cholangiocarcinoma and pancreatic cancer can be CK 20-/CK 7+ or CK 7+ with focal positivity for CK 20. Eighty-five percent of lung cancers are positive for CK 7, and the use of thyroid transcription factor-1 (TTF-1) and surfactant apoprotein can further help distinguish lung primary tumors from other CK 7+ tumors.[13,14] Approximately 68% of lung adenocarcinomas and 25% of squamous cell lung cancers stain positive for TTF-1.

Distinguishing mesothelioma from adenocarcinoma can sometimes prove to be quite challenging.[15] Immunohistochemical analysis, rather than electron microscopy, is increasingly being used to diagnose mesothelioma; calretinin, Wilms' tumor-1, and mesothelin may be useful markers. If the morphologic characteristics are unclear, a combination of immunohistochemical markers such as MOC-31 (or Ber-EP4), estrogen receptor, calretinin, and Wilms' tumor-1 are used to help distinguish mesothelioma of the peritoneum from serous papillary carcinomas.[16]

Expression of hepatocyte paraffin 1 antibody is found primarily in benign and malignant hepatocytes and can aid in the immunohistochemical diagnosis of hepatocellular carcinoma.[17,18] Gross cystic disease fluid protein 15 (GCDFP-15), a 15-kDa-monomer protein, is a marker of apocrine differentiation that is specifically expressed in breast carcinomas; expression is detected in 62%–72% of cases.[19–22] Uroplakin III, high-molecular weight cytokeratin, thrombomodulin, and CK 20 are the markers typically used for diagnoses in cases suspected to have a urothelial origin.[23,24] The nuclear transcription factor caudal-related homeobox 2 (CDX-2), which is the product of a homeobox gene necessary for intestinal organogenesis, is expressed in normal colonic epithelia and most colo-

Table 1. Immunoperoxidase stains used in the differential diagnosis of CUP.

Stain	Primary tumor
ER, PR, GCDFP-15, Her-2/neu	Breast cancer
TTF, CK 7, surfactant proteins	Lung cancer
Chromogranin, synaptophysin, neuron-specific enolase	Neuroendocrine tumor
β–Hcg, α-fetoprotein	Germ cell tumor
CK 7, CK 20, uroplakin III	Urothelial malignancy
Calretinin	Mesothelioma
Hep Par-1	Hepatocellular carcinoma
CK 7, CK 20, CDX-2, CEA	Colorectal cancer

Abbreviations: CDX = caudal-related homeobox; CEA = carcinoembryonic antigen; CK = cytokeratin; ER = estrogen receptor; GCDFP = gross cystic disease fluid protein; Hcg = human chorionic gonadotropin; Hep Par = hepatocyte paraffin; PR = progesterone receptor; TTF = thyroid transcription factor.

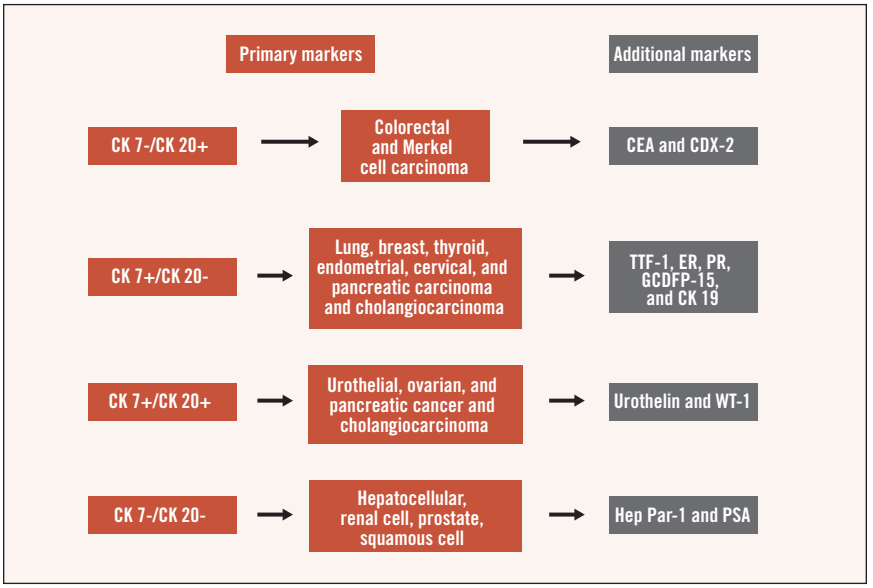

Figure 1. Immunohistochemical analysis of CUP based on cytokeratin (CK) status.
Abbreviations: CDX = caudal-related homeobox; CEA = carcinoembryonic antigen; ER = estrogen receptor; GCDFP = gross cystic disease fluid protein; Hep Par = hepatocyte paraffin; PR = progesterone receptor; PSA = prostate specific antigen; WT = Wilms' tumor

rectal adenocarcinomas and is often used to aid in diagnosing gastrointestinal adenocarcinoma.[25]

Figure 1 shows a simple algorithm for immunohistochemical analysis of adenocarcinoma CUP based on CK status. Additional tests to further define the tumor lineage are shown in Table 1. Although immunohistochemical markers can help select appropriate therapy when used in conjunction with clinical and imaging findings, the markers are not very specific and one should thus avoid overinterpretation of the testing results.

Serum Tumor Markers and Cytogenetics

Men with adenocarcinoma and bone metastasis should undergo a PSA test. Beta-human chorionic gonadotropin and alpha-fetoprotein levels usually are measured in cases of undifferentiated or poorly differentiated carcinoma (especially when a midline tumor is present) to evaluate for extragonadal germ cell tumors. Most tumor markers, including carcinoembryonic antigen, CA-125, CA 19-9, and CA 15-3, are not specific and are thus not helpful in determining the site of the primary tumor.[26,27] Similarly, in our view, cytogenetic analysis is not helpful now that immunohistochemical tests are widely used and can help differentiate a lymphoma from epithelial cancers. In a study by Motzer and colleagues,[28] 40 patients with poorly differentiated carcinoma and CUP underwent cytogenetic analysis. Seventeen patients (42%) were diagnosed by genetic analysis, including 12 (30%) with cytogenetic changes characteristically seen in germ cell tumors (eg, isochromosome 12p, increased 12p copy number, or deletion of the long arm of chromosome 12). Pantou and colleagues[29] studied 20 CUP samples, and in 5 patients (4 with lymphoma and 1 with Ewing sarcoma), and cytogenetics aided in the diagnosis of the primary tumor. The other samples had multiple complex cytogenetic patterns.

Interpreting the results of older studies is difficult. At our institution, cytogenetic and B cell and T cell gene rearrangement studies are occasionally requested to rule out lymphoma when the index of suspicion for lymphoma is high and when the immunohistochemical results are equivocal, a scenario sometimes encountered with poorly differentiated neoplasms.

IMAGING STUDIES IN CUP

CT and Mammography

Computed tomography of the abdomen and pelvis is routinely performed in CUP cases to locate the primary tumor, evaluate the extent of disease, and select the most favorable biopsy site. In the 1980s, McMillan and colleagues[30] retrospectively studied the role of abdominal CT in 46 CUP patients with metastatic adenocarcinoma or undifferentiated carcinoma. The primary tumor site was ultimately identified in 21 patients. CT of the abdomen detected it in 16 of these patients and demonstrated additional and often unsuspected metastatic disease in 65%. CT was superior to sonography and contrast studies of the urinary and gastrointestinal tracts. In a study by Abbruzzese and colleagues,[31] latent primary tumors were found in 179 of 879 CUP patients (20%), though in the era of sophisticated imaging, this number is low (2%–3%). In practice, CT of the chest, abdomen, and pelvis is routinely performed in all patients. Mammography should be performed in all women who present with metastatic adenocarcinoma.

Conventional work up for cervical CUP (typically neck adenopathy) presenting with squamous cell cancer includes CT or magnetic resonance imaging (MRI) and panendoscopy. A superficial biopsy of the tonsil can miss a small primary tumor, and an ipsilateral (or preferably bilateral) tonsillectomy has been recommended for all patients presenting with squamous cell cervical CUP.[32,33]

Positron Emission Tomography

The role of positron emission tomography (PET) in the diagnostic algorithm of patients with disseminated (noncervical) CUP remains controversial, with most of the data being retrospective. The majority of the PET studies in CUP involve patients with squamous cell cancer and cervical adenopathy, a subgroup of patients in whom the utility of PET has been well demonstrated. Primary tumors have been identified in approximately 21%–30% of cervical CUP patients; however, these findings are from small studies.[34–36] Most physicians agree that 18F-fluorodeoxyglucose (FDG)-PET is useful in this patient population, since it may help guide the biopsy, determine the extent of disease, facilitate the appropriate treatment (including radiation fields), and help with disease surveillance.

Rusthoven and colleagues[37] reviewed 16 FDG-PET studies published between 1994 and 2003 that involved a total of 302 patients with CUP cervical metastases. The conventional work-up included panendoscopy or CT/MRI. In 10 of the 16 studies, both diagnostic techniques (panendoscopy and CT/MRI) were performed before the diagnosis had been made. The overall sensitivity, specificity, and accuracy rates of FDG-PET in detecting unknown primary tumors were 88.3%, 74.9%, and 78.8%, respectively. FDG-PET detected approximately 25% of tumors that were not found on conventional work-up and detected previously undetected regional or distant metastases in 27% of patients.

In addition, in two small retrospective studies, PET detected the primary tumor in 20% of non-cervical CUP patients.[38,39] At our institution, we typically use PET-CT in patients with cervical CUP, patients with solitary metastatic disease (because treatment depends on the extent of disease), patients with an iodine allergy, and patients with no evidence of disease who are undergoing postsurgical adjuvant therapy (because PET results may influence treatment planning and prognosis).

In the near future, especially with the addition of intravenous contrast to PET-CT scanning, one can expect greater use of PET-CT scans in the CUP setting, and large well-designed studies of the cost-effectiveness of PET would be useful.

MRI

Magnetic resonance imaging is a recognized method for assessing isolated axillary lymph node metastases and suspected occult primary breast carcinoma (after negative mammography and sonography findings). Olson and colleagues[40] studied 40 women with metastatic disease of the axillary nodes and no primary tumor on mammography. In 28 women (70%), a pri-

mary tumor was found on MRI using a dedicated breast coil. Five of the 12 women with negative breast MRI findings underwent modified radical mastectomy; in four, no tumor was found in the mastectomy specimen. These findings suggest that MRI is effective at detecting breast cancer in up to 75% of women presenting with axillary adenopathy. MRI of the breast also can influence surgical management, as suggested by the finding in this study that negative breast MRI results are associated with a low-yield at mastectomy.

ROLE OF DNA MICROARRAY AND REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION IN DIAGNOSING CUP

Developing therapeutic strategies, especially those involving targeted therapy, can be challenging in CUP cases, and use of DNA microarrays and reverse transcription polymerase chain reaction (RT-PCR) techniques promise to ultimately be of help in this regard.

Gene expression studies require a training set of gene profiles of known cancers that represents the tumor types that are thought to be present in the study population. Neural network programs have been used to develop predictive algorithms from the gene expression profiles. Typically, a set of gene profiles from known cancers (preferably from metastatic sites) is used to train the software. The program can then be used to predict the origin of the test tumor. Comprehensive gene expression databases that have become available for common cancer types may be useful for CUP. Investigators have used expression data from normal differentiated tissues to identify conserved expression profiles found in malignant tissue and thus predict the tissue of origin.[41–44]

Su and colleagues[44] described the use of large-scale RNA profiling and supervised machine learning algorithms to construct a first-generation molecular classification system for the 11 cancers that account for 70% of all cancer-related deaths. The predictor gene subsets included genes with expression that was specific to the tissue of origin and genes with elevated expression in cancer. The authors used a set of 100 primary carcinomas from 10 common tumor types. A predictive algorithm was developed using 110 of the 9,198 genes that were minimally expressed in these tumors. The algorithm was then tested against additional 75 blinded samples, including 12 metastatic samples, and accurately identified the tumor of origin in more than 90% of cases. Eleven of the 12 metastasis test cases were classified correctly.

Tothill and colleagues[45] used data generated from both quantitative PCR (low-density array to allow the use of both fresh-frozen and formalin-fixed paraffin-embedded tissue) and a microarray to train and validate a cross-platform support vector machine (SVM) model to detect the primary cancer. They applied SVM classifiers to 13 cases of CUP; in 11 cases, the predictions were supported by data from the patients' clinical histories.

However, because the primary tumor site is unknown in CUP, validating the primary tumor site can be challenging; predictions must be supported by clinical and pathologic findings. Prospective indirect validation trials are currently evaluating the utility of molecular studies in CUP.

TREATMENT

General Considerations

The results of CUP clinical trials are difficult to interpret given the heterogeneity of the cancers involved. In addition, no multi-institutional trials have been conducted involving specific subsets of CUP. The median survival duration of patients with disseminated CUP is approximately 6 to 10 months. Systemic chemotherapy is the main treatment modality for most patients, but surgery, radiation therapy, and even periods of observation are important. Prognostic factors include performance status, locations of and number of metastases, response to chemotherapy, and serum lactate dehydrogenase level. Culine and colleagues[46] recently developed and retrospectively validated a prognostic model that includes performance status and serum lactate dehydrogenase levels, allowing patients to be assigned to one of two subgroups with divergent outcomes. Further prospective trials using this prognostic model are warranted. Clinically, some CUP diagnoses fall in favorable prognostic subsets and are discussed below. Others, including disseminated CUP, have a less favorable prognosis.

Treatment of Prognostically Favorable Subsets of CUP

Favorable subgroups are important to identify, because specific treatment may significantly extend survival.

Isolated Axillary Adenopathy With Adenocarcinoma or Carcinoma in Women

Women with isolated axillary adenopathy and adenocarcinoma or carcinoma should be treated for stage II or III breast cancer and are candidates for breast MRI if their mammography and sonography results are negative. If breast MRI results are positive, lumpectomy and radiation therapy to the ipsilateral breast should be considered for local disease control.[47] If the clinical and imaging presentations suggest breast cancer, axillary lymph node dissection followed by chemotherapy and radiation therapy (and hormonal therapy if appropriate) is the standard approach. At our institution, we often use neoadjuvant systemic therapy followed by surgery, especially in patients with bulky nodal disease. Immunohistochemical analysis of estrogen and progesterone receptors and Her-2/neu can help determine the appropriate treatment.

Peritoneal Carcinomatosis Suggestive of Primary Peritoneal Carcinoma in Women

Primary peritoneal papillary serous carcinoma (PPSC) refers to CUP with carcinomatosis and the pathologic and laboratory (elevated CA-125 antigen) characteristics of ovarian cancer but no ovarian primary tumor identified on transvaginal sonography or laparotomy. Patients with PPSC are candidates for ovarian cancer treatment — ie, cytoreductive surgery followed by adjuvant taxane- and platinum-based chemotherapy. In a study by Pentheroudakis and colleagues,[48] women with peritoneal carcinomatosis who had undergone surgical debulking and chemotherapy experienced median progression-free and overall survival durations of 7 and 15 months, respectively (median follow-up, 60 months).

Midline Adenopathy or Poorly Differentiated or Undifferentiated Carcinoma

Men with poorly differentiated or undifferentiated carcinoma that presents as midline adenopathy should be evaluated for extragonadal germ cell malignancy. Cytogenetic analysis (for isochromosome 12p) was used in the past to diagnose extranodal germ cell cancer, but is rarely used now. In the past, patients with extragonadal germ cell cancer were sometimes misdiagnosed with CUP. Some patients with poorly differentiated or undifferentiated carcinoma that presents as midline adenopathy exhibit a response to platinum-based combination chemotherapy, even without a clear diagnosis of germ cell cancer. A small number of long-term survivors have been reported.

Low-Grade Neuroendocrine Carcinoma

Patients with low-grade neuroendocrine carcinoma may have an indolent disease course; thus, treatment decisions are based on symptoms and tumor bulk. It is important to differentiate between low-grade and high-grade neuroendocrine CUP (high-grade neuroendocrine cancers have a high mitotic index, necrosis, and hemorrhage on pathologic evaluation). Patients with low-grade neuroendocrine cancers are often treated with somatostatin analogs alone for hormone-related symptoms (eg, diarrhea, flushing, and nausea). Specific local therapies (embolization) or systemic therapy is indicated if the patient is symptomatic with significant tumor growth or if the hormone-related symptoms cannot be controlled with endocrine therapy.

Cervical Adenopathy With Squamous Cell Carcinoma

Patients with cervical adenopathy with squamous cell carcinoma should undergo triple endoscopy with biopsies of inconspicuous sites, a unilateral or bilateral tonsillectomy, and CT or PET-CT of the neck and chest to search for the primary tumor and determine tumor stage. Patients with early stage disease are candidates for node dissection and radiation therapy, which can result in long-term survival. The utility of chemotherapy in these patients is unknown, though chemoradiation therapy or induction chemotherapy is often used and is beneficial in bulky N2 and N3 disease.

Solitary Metastases

Some patients with solitary CUP metastases are candidates for aggressive trimodality management, which can result in prolonged disease-free survival and even cure. In selected patients who present with solitary liver or other solid organ CUP metastases, our institutional approach is to first use neoadjuvant chemotherapy or chemoradiation therapy instead of surgery, allowing us to gauge the cancer's aggressiveness. Patients with stable or responsive disease are most likely to experience a favorable oncologic outcome with surgery (this is particularly important given the heterogeneity of CUP and the potential morbidity of surgery). In addition, neoadjuvant chemotherapy is used to treat micrometastatic disease and downstage the lesion to maximize the potential for a margin-negative resection.

We do not advocate this approach in all patients with solitary metastatic CUP or suggest that it should constitute standard of care in this setting. Since the role of neoadjuvant therapy in this setting is unproven, definitive local therapy can also be considered as standard treatment. A prospective clinical trial of preoperative chemotherapy and surgery for solitary nodal and visceral metastasis is warranted; however, given the sample size needed, such a study would likely not be feasible.

Treatment of Prognostically Unfavorable Subsets of CUP

Median survival for patients with CUP and disseminated disease is 8 to 10 months. Performance status plays a critical role in treatment planning. Imaging and pathology evaluation helps select the best therapy for CUP patients. CUP subsets with relatively unfavorable prognosis are discussed here.

Non-PPSC Peritoneal Carcinomatosis

Presentation of non-PPSC peritoneal carcinomatosis as CUP is not uncommon. Gastric, appendicular, colon, and pancreatic cancers, as well as cholangiocarcinoma are all possible primary tumors in these cases. Imaging, endoscopy, and pathologic evaluations help with the overall evaluation.

In patients with carcinomatosis and an immunohistochemical profile favoring colon cancer (CK 7-/CK 20+ and CDX-2+), use of a colon cancer regimen is a reasonable treatment approach, though data comparing response rates and survival using this approach to outcomes with "conventional CUP" regimens are lacking. The differential diagnosis for signet ring cell adenocarcinoma with carcinomatosis is broad in cases in which an immunohistochemical analysis has ruled out colon cancer. Possible primary tumors include gastric, pancreatic, and appendicular tumors, cholangiocarcinoma, and, in women, lobular breast cancer. A calretinin stain can help differentiate between peritoneal mesothelioma and adenocarcinoma. In addition, pseudomyxoma peritonii may present as CUP; these patients may be candidates for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Liver Metastases and CUP

Isolated liver metastases are common in CUP adenocarcinoma. The differential diagnosis includes hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and metastatic adenocarcinoma. Unfortunately, no specific immunohistochemical or serum markers are effective at differentiating between cholangiocarcinoma and metastatic adenocarcinoma. Risk factors, imaging, and pathologic findings can guide systemic therapy decisions.

Systemic Therapy for CUP

Traditionally, cisplatin-based combination chemotherapy regimens have been used to treat patients with CUP. In a phase II study by Greco and Hainsworth,[49] 55 CUP patients (51 of whom were chemotherapy-naïve) were treated with paclitaxel, carboplatin, and oral etoposide every 3 weeks. The overall response rate was 47%, and the median overall survival duration was 13.4 months. Briasoulis and colleagues[50] reported similar results in 77 CUP patients treated with paclitaxel and carboplatin. Patients with nodal or pleural disease and peritoneal carcinomatosis had higher response rates (compared with patients with visceral disseminated disease) and overall survival durations of 13 and 15 months, respectively.

More recent studies have incorporated newer agents, such as gemcitabine, irinotecan, and targeted agents. In a phase II randomized trial by Culine and colleagues,[51] 80 patients received gemcitabine plus cisplatin or irinotecan plus cisplatin. Among 78 evaluable patients, objective responses were observed in 21 (55%) in the gemcitabine/cisplatin arm and 15 (38%) in the irinotecan/cisplatin arm. The median survival durations were 8 and 6 months, respectively (median follow-up, 22 months).

The utility of second-line chemotherapy in CUP is unclear. Hainsworth and colleagues[52] reported on 39 patients treated with gemcitabine in a salvage setting (most patients' disease had not responded to a previous regimen containing platinum and a taxane, and only 21% of patients had ever experienced a response to previous therapy). The overall partial response rate was 8%, and 25% of patients experienced a minor response or stable disease with improved symptoms. The median time to progression for patients who experience a partial response or stable disease was 5 months, and the treatment was well tolerated.

Preliminary data on combination targeted therapy are available. Hainsworth and colleagues[53] determined the effectiveness of bevacizumab and erlotinib in 51 patients, 25% of whom were chemotherapy naïve with advanced bone or liver metastases and 75% of whom had been treated with one or two chemotherapy regimens. Responses were noted in 4 patients (8%), and 30 patients (59%) experienced stable disease or a minor response. The median overall survival duration was 8.9 months, with 42% of patients alive at 1 year.

An algorithm based on immunohistochemical analysis and clinical presentation may facilitate selection of treatment in patients with CUP, and this approach currently is being evaluated at our institution. For example, patients with TTF-1–positive cancers can be treated with a lung cancer regimen, patients with CK 20+/CK 7- cancers may receive colorectal cancer regimens, and those with cancers suggestive of pancreaticobiliary origin can be treated with gemcitabine-based regimens. A randomized trial comparing "standard" CUP chemotherapy vs. chemotherapy tailored to pathology (including DNA microarray or RT-PCR data) would be of considerable interest.

DISCUSSION

A focused search for the primary tumor is recommended in CUP cases. Identifying patients with prognostically favorable disease is important, since they may have substantial benefit from directed treatment and experience prolonged survival. However, for most CUP patients, resistance to available cytotoxic therapy occurs frequently and prognosis is grim. The response rates among known cancer types have incrementally improved over the past decade; thus, we anticipate higher overall response rates with new targeted regimens for selected CUP patients. With a robust immunohistochemical panel (directed approach) and the use of emerging molecular data, we hope to create a tailored treatment algorithm for CUP patients. Whether CUP has a molecular genotype-phenotype that is distinct from metastases of known primary tumors remains to be elucidated. The identification of specific CUP-related molecular and biochemical targets may help us identify appropriate targeted agents for individual patients with this disease.

REFERENCES

1. Abbruzzese JL, Lenzi R, Raber MN, et al: The biology of unknown primary tumors. *Semin Oncol* 20:238–243, 1993
2. Bugat R, Bataillard A, Lesimple T, et al: Summary of the standards, options and recommendations for the management of patients with carcinoma of unknown primary site (2002). *Br J Cancer* 89(suppl 1):S59–S66, 2003
3. Bell CW, Pathak S, Frost P: Unknown primary tumors: establishment of cell lines, identification of chromosomal abnormalities, and implications for a second type of tumor progression. *Cancer Res* 49:4311–4315, 1989
4. Bar-Eli M, Abbruzzese JL, Lee-Jackson D, et al: p53 gene mutation spectrum in human unknown primary tumors. *Anticancer Res* 13:1619–1623, 1993
5. Briasoulis E, Tsokos M, Fountzilas G, et al: Bcl2 and p53 protein expression in metastatic carcinoma of unknown primary origin: biological and clinical implications. A Hellenic Co-operative Oncology Group study. *Anticancer Res* 18:1907–1914, 1998
6. Hainsworth JD, Lennington WJ, Greco FA: Overexpression of Her-2 in patients with poorly differentiated carcinoma or poorly differentiated adenocarcinoma of unknown primary site. *J Clin Oncol* 18:632–635, 2000
7. Naresh KN: Do metastatic tumours from an unknown primary reflect angiogenic incompetence of the tumour at the primary site?—a hypothesis. *Med Hypotheses* 59:357–360, 2002
8. Karavasilis V, Malamou-Mitsi V, Briasoulis E, et al: Angiogenesis in cancer of unknown primary: clinicopathological study of CD34, VEGF and TSP-1. *BMC Cancer* 5:25, 2005
9. Hillen HF, Hak LE, Joosten-Achjanie SR, et al: Microvessel density in unknown primary tumors. *Int J Cancer* 74:81–85, 1997
10. Varadhachary GR, Abbruzzese JL, Lenzi R: Diagnostic strategies for unknown primary cancer. *Cancer* 100:1776-1785, 2004
11. van Krieken JH: Prostate marker immunoreactivity in salivary gland neoplasms. A rare pitfall in immunohistochemistry. *Am J Surg Pathol* 17:410–414, 1993
12. Rubin BP, Skarin AT, Pisick E, et al: Use of cytokeratins 7 and 20 in determining the origin of metastatic carcinoma of unknown primary, with special emphasis on lung cancer. *Eur J Cancer Prev* 10:77-82, 2001
13. Bejarano PA, Baughman RP, Biddinger PW, et al: Surfactant proteins and thyroid transcription factor-1 in pulmonary and breast carcinomas. *Mod Pathol* 9:445–452, 1996
14. Tan D, Li Q, Deeb G, et al: Thyroid transcription factor-1 expression prevalence and its clinical implications in non-small cell lung cancer: a high-throughput tissue microarray and immunohistochemistry study. *Hum Pathol* 34:597–604, 2003
15. Abutaily AS, Addis BJ, Roche WR: Immunohistochemistry in the distinction between malignant mesothelioma and pulmonary adenocarcinoma: a critical evaluation of new antibodies. *J Clin Pathol* 55:662–668, 2002
16. Ordonez NG: The diagnostic utility of immunohistochemistry and electron microscopy in distinguishing between peritoneal mesotheliomas and serous carcinomas: a comparative study. *Mod Pathol* 19:34–48, 2006
17. Lau SK, Prakash S, Geller SA, et al: Comparative immunohistochemical profile of hepatocellular carcinoma, cholangiocarcinoma, and metastatic adenocarcinoma. *Hum Pathol* 33:1175–1181, 2002
18. Maitra A, Murakata LA, Albores-Saavedra J: Immunoreactivity for hepatocyte paraffin 1 antibody in hepatoid adenocarcinomas of the gastrointestinal tract. *Am J Clin Pathol* 115:689–694, 2001
19. Clark JW, Snell L, Shiu RP, et al: The potential role for prolactin-inducible protein (PIP) as a marker of human breast cancer micrometastasis. *Br J Cancer* 81:1002–1008, 1999
20. Kaufmann O, Deidesheimer T, Muehlenberg M, et al: Immunohistochemical differentiation of metastatic breast carcinomas from metastatic adenocarcinomas of other common primary sites. *Histopathology* 29:233–240, 1996
21. Satoh F, Umemura S, Osamura RY: Immunohistochemical analysis of GCDFP-15 and GCDFP-24 in mammary and non-mammary tissue. *Breast Cancer* 7:49–55, 2000
22. Wick MR, Lillemoe TJ, Copland GT, et al: Gross cystic disease fluid protein-15 as a marker for breast cancer: immunohistochemical analysis of 690 human neoplasms and comparison with alpha-lactalbumin. *Hum Pathol* 20:281–287, 1989
23. Kaufmann O, Volmerig J, Dietel M: Uroplakin III

is a highly specific and moderately sensitive immunohistochemical marker for primary and metastatic urothelial carcinomas. *Am J Clin Pathol* 113:683–687, 2000

24. Parker DC, Folpe AL, Bell J, et al: Potential utility of uroplakin III, thrombomodulin, high molecular weight cytokeratin, and cytokeratin 20 in noninvasive, invasive, and metastatic urothelial (transitional cell) carcinomas. *Am J Surg Pathol* 27:1–10, 2003
25. Barbareschi M, Murer B, Colby TV, et al: CDX-2 homeobox gene expression is a reliable marker of colorectal adenocarcinoma metastases to the lungs. *Am J Surg Pathol* 27:141–149, 2003
26. Milovic M, Popov I, Jelic S: Tumor markers in metastatic disease from cancer of unknown primary origin. *Med Sci Monit* 8:MT25–MT30, 2002
27. Pavlidis N, Kalef-Ezra J, Briassoulis E, et al: Evaluation of six tumor markers in patients with carcinoma of unknown primary. *Med Pediatr Oncol* 22:162–167, 1994
28. Motzer RJ, Rodriguez E, Reuter VE, et al: Molecular and cytogenetic studies in the diagnosis of patients with poorly differentiated carcinomas of unknown primary site. *J Clin Oncol* 13:274–282, 1995
29. Pantou D, Tsarouha H, Papadopoulou A, et al: Cytogenetic profile of unknown primary tumors: clues for their pathogenesis and clinical management. *Neoplasia* 5:23–31, 2003
30. McMillan JH, Levine E, Stephens RH: Computed tomography in the evaluation of metastatic adenocarcinoma from an unknown primary site. A retrospective study. *Radiology* 143:143–146, 1982
31. Abbruzzese JL, Abbruzzese MC, Lenzi R, et al: Analysis of a diagnostic strategy for patients with suspected tumors of unknown origin. *J Clin Oncol* 13:2094–2103, 1995
32. Koch WM, Bhatti N, Williams MF, et al: Oncologic rationale for bilateral tonsillectomy in head and neck squamous cell carcinoma of unknown primary source. *Otolaryngol Head Neck Surg* 124:331–333, 2001
33. Randall DA, Johnstone PA, Foss RD, et al: Tonsillectomy in diagnosis of the unknown primary tumor of the head and neck. *Otolaryngol Head Neck Surg* 122:52–55, 2000
34. Johansen J, Eigtved A, Buchwald C, et al: Implication of 18F-fluoro-2-deoxy-D-glucose positron emission tomography on management of carcinoma of unknown primary in the head and neck: a Danish cohort study. *Laryngoscope* 112: 2009–2014, 2002
35. Jungehulsing M, Scheidhauer K, Damm M, et al: 2[F]-fluoro-2-deoxy-D-glucose positron emission tomography is a sensitive tool for the detection of occult primary cancer (carcinoma of unknown primary syndrome) with head and neck lymph node manifestation. *Otolaryngol Head Neck Surg* 123:294–301, 2000
36. Regelink G, Brouwer J, de Bree R, et al: Detection of unknown primary tumours and distant metastases in patients with cervical metastases: value of FDG-PET versus conventional modalities. *Eur J Nucl Med Mol Imaging* 29:1024–1030, 2002
37. Rusthoven KE, Koshy M, Paulino AC: The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. *Cancer* 101:2641–2649, 2004
38. Alberini JL, Belhocine T, Hustinx R, et al: Whole-body positron emission tomography using fluorodeoxyglucose in patients with metastases of unknown primary tumours (CUP syndrome). *Nucl Med Commun* 24:1081–1086, 2003
39. Gutzeit A, Antoch G, Kuhl H, et al: Unknown primary tumors: detection with dual-modality PET/CT—initial experience. *Radiology* 234: 227–234, 2005
40. Olson JA Jr, Morris EA, Van Zee KJ, et al: Magnetic resonance imaging facilitates breast conservation for occult breast cancer. *Ann Surg Oncol* 7:411–415, 2000
41. Bhattacharjee A, Richards WG, Staunton J, et al: Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. *Proc Natl Acad Sci USA* 98:13790–13795, 2001
42. Dennis JL, Hvidsten TR, Wit EC, et al: Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm. *Clin Cancer Res* 11:3766–3772, 2005
43. Dennis JL, Vass JK, Wit EC, et al: Identification from public data of molecular markers of adenocarcinoma characteristic of the site of origin. *Cancer Res* 62:5999–6005, 2002
44. Su AI, Welsh JB, Sapinoso LM, et al: Molecular classification of human carcinomas by use of gene expression signatures. *Cancer Res* 61: 7388–7393, 2001
45. Tothill RW, Kowalczyk A, Rischin D, et al: An expression-based site of origin diagnostic method designed for clinical application to cancer of unknown origin. *Cancer Res* 65:4031–4040, 2005
46. Culine S, Kramar A, Saghatchian M, et al: Development and validation of a prognostic model to predict the length of survival in patients with carcinomas of an unknown primary site. *J Clin Oncol* 20:4679–4683, 2002
47. Vlastos G, Jean ME, Mirza AN, et al: Feasibility of breast preservation in the treatment of occult primary carcinoma presenting with axillary metastases. *Ann Surg Oncol* 8:425–431, 2001
48. Pentheroudakis G, Briasoulis E, Karavassilis V, et al: Chemotherapy for patients with two favourable subsets of unknown primary carcinoma: active, but how effective? *Acta Oncol* 44:155–160, 2005
49. Greco FA, Hainsworth JD: One-hour paclitaxel, carboplatin, and extended-schedule etoposide in the treatment of carcinoma of unknown primary site. *Semin Oncol* 24:S19–101–S19–105, 1997
50. Briasoulis E, Kalofonos H, Bafaloukos D, et al: Carboplatin plus paclitaxel in unknown primary carcinoma: a phase II Hellenic Cooperative Oncology Group study. *J Clin Oncol* 18:3101–3107, 2000
51. Culine S, Lortholary A, Voigt JJ, et al: Cisplatin in combination with either gemcitabine or irinotecan in carcinomas of unknown primary site: results of a randomized phase II study—trial for the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01). *J Clin Oncol* 21:3479–3482, 2003
52. Hainsworth JD, Burris HA III, Calvert SW, et al: Gemcitabine in the second-line therapy of patients with carcinoma of unknown primary site: a phase II trial of the Minnie Pearl Cancer Research Network. *Cancer Invest* 19:335–339, 2001
53. Hainsworth JD, Spigel DR, Thompson DS, et al: Bevacizumab plus erlotinib in patients (pts) with carcinoma of unknown primary site: a phase II trial of the Minnie Pearl Cancer Research Network. 2006 ASCO Annual Meeting Proceedings. *J Clin Oncol* 24:18S, 2006 (abstr 3033)

Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.