Management of Patients With Cancer of Unknown Primary Site

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Cancer of unknown primary site represents approximately 3% to 5% of all new cancer diagnoses. Adenocarcinomas account for 60% of all unknown primary cancers and poorly differentiated carcinomas or

Introduction

Cancer of unknown primary site accounts for 3% to 5% of all cancer diagnoses.[1] This syndrome occurs with equal frequency in men and women and increases in incidence with advancing age. Numerous clinical presentations and histologic tumor characteristics are represented in this heterogeneous group of patients. Common sites of metastases include the liver, bone, lung, lymph nodes, pleura, and brain. The majority of patients have metastases present in two or more sites.[2] Patients are diagnosed with cancer of unknown primary site after an initial standard evaluation fails to identify a primary tumor site.

Historically, patients with an unknown primary tumor have responded poorly to empiric therapy, and median survival from diagnosis has usually been less than 8 months. The limited activity of early chemotherapeutic regimens and short median survival have contributed to clinical nihilism about patients with cancer of unknown primary site.

A number of patient subsets with specific treatment implications have now been described, however. These subsets, identified by specific clinical or pathologic criteria, account for approximately 40% of all patients with unknown primary tumors. In the remaining patients, recent studies of empiric taxane-containing therapies have produced higher response rates, and have probably extended survival. Ongoing evaluations of other new regimens and approaches to the treatment of cancer of unknown primary may result in additional treatment advances.

Diagnosis and Evaluation

Approximately 60% of patients with cancer of unknown primary site have well-differentiated or moderately well-differentiated adenocarcinoma. Poorly differentiated carcinomas or poorly differentiated adenocarcinomas are diagnosed in approximately 30% of patients. Squamous cell carcinomas and poorly differentiated neoplasms account for 5% of diagnoses. Clinical presentation, evaluation, prognosis, and treatment options differ for these four histologically distinct groups. The presence of specific clinical features or the use of specialized pathologic studies can identify subsets within these broad categories of patients who may benefit from tumor-specific therapy.

Clinical Evaluation

In most patients, the clinical evaluation, including the search for the primary site, should be brief and focused. A careful history should be taken and a complete physical examination should be performed (including pelvic and rectal examinations), with routine laboratory evaluation (hematologic and chemistry profiles), chest radiography, and computed tomography (CT) of the abdomen and pelvis.[2] Computed tomographic scans of the abdomen may identify a primary site in 10% to 35% of patients; CT scans may also locate additional sites of metastatic disease.[3,4] Tumors identified by CT scans of the abdomen and pelvis include those arising from the pancreas, kidney, hepatobiliary tract, and ovary.

Additional procedures (eg, radiologic imaging and/or endoscopic examinations) are warranted to evaluate specific presenting signs or symptoms. Positron emission tomography (PET), performed with fluorine-18-deoxyglucose, is a noninvasive technique that has identified primary sites in a few patients, although its role in the evaluation of patients with cancer of unknown primary site is incompletely defined.[5,6]

Certain additional diagnostic evaluations should be performed in specific patient subsets. For example, mammography should be performed in women with clinical features suggestive of metastatic breast cancer. All men with adenocarcinoma of unknown primary site should have their
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serum prostate-specific antigen (PSA) levels measured, as well as PSA staining of the biopsy
specimen. Serum levels of human chorionic gonadotropin (HCG) and alpha-fetoprotein (AFP) should
be measured in young men with poorly differentiated carcinoma.
The diagnostic yield of other additional diagnostic procedures is low[7,8] (Table 1) and can add
considerable expense to the initial evaluation. Extensive radiologic or endoscopic investigations of
asymptomatic areas are rarely useful in identifying a primary site. Measurement of various commonly used serum tumor markers (eg, carcinoembryonic antigen [CEA],
cancer antigen 15-3 [CA 15-3], cancer antigen 125 [CA-125], and cancer antigen 19-9 [CA 19-9]) also
is not useful in providing clues to the location of the primary site. All of these markers are frequently
raised in patients with carcinoma of unknown primary site, and thus, provide no diagnostic or
prognostic information. Modest elevations of HCG or AFP (ie, levels of either marker < 100) are
also of no diagnostic or prognostic utility in this patient population. If levels of any of these
markers are elevated, serial measurement may be useful in assessing response to treatment.

Pathologic Evaluation
An accurate pathologic evaluation of tumor tissue is an essential part of the diagnostic process. A
biopsy of the most accessible lesion should be performed. A fine-needle biopsy is least invasive but
may not yield enough tissue for specialized pathologic studies, which are required for all patients
with poorly differentiated tumors. Close collaboration with the pathologist is therefore necessary to
ensure that optimal diagnostic studies are performed. The pathologist should be informed about all
of the clinical information to assist in the selection of specialized pathologic studies.
Light microscopic examination results in the identification of several subgroups, including poorly
differentiated neoplasms, well-differentiated and moderately well-differentiated adenocarcinomas,
squamous cell carcinomas, and poorly differentiated carcinomas (with or without features of
adenocarcinomas). Histochemical staining for mucin may facilitate identification of some
adenocarcinomas.[11]

In patients with well-differentiated or moderately differentiated adenocarcinoma, further pathologic
studies rarely identify a primary site and are only indicated in selected patient subgroups. Staining
for PSA occasionally identifies a prostate primary site in men with metastatic adenocarcinoma, and
positive staining for estrogen/progesterone receptors is useful in women with clinical features
compatible with metastatic breast cancer.
As opposed to their limited utility in patients with adenocarcinoma, additional pathologic studies
frequently add useful information to the evaluation of poorly differentiated tumors.
Immunocytochemical stains are now widely available and should be routinely performed. Although
definitive diagnoses can be made only in a minority of patients, a number of diagnoses can be
suggested with this technique, including lymphoma, melanoma, sarcoma, and neuroendocrine
carcinoma (Table 2). Several of these diagnoses have specific therapeutic implications.
A number of “tumor-specific” antibodies or antibody panels have been evaluated. However, none of
these is sufficiently specific to reliably identify a primary site.[12-15]
Electron microscopy is also a valuable tool in the evaluation of poorly differentiated tumors. Since it
is less widely available and often requires rebiopsy with special tissue preparation, electron
microscopy should be reserved for use in tumors of uncertain lineage following immunoperoxidase
studies. Definitive diagnoses of lymphoma, neuroendocrine tumors, melanoma, and a variety of
sarcomas is possible with electron microscopy.

Therapy
When a primary site is definitively identified by either clinical or pathologic evaluation, treatment
should proceed according to the guidelines for that type of cancer. In the large majority of patients,
however, no primary site can be identified. In these patients, it is probably best to avoid the
temptation to “guess” at a primary site based on either suggestive clinical or pathologic features.
For example, patients with mucin-positive adenocarcinoma involving the liver may have an
unidentified gastrointestinal primary, and yet empiric treatment with gastrointestinal regimens (eg,
fluorouracil [5-FU]/leucovorin) has shown very little benefit in this group.[16] Therefore, empiric treatment for carcinoma of
unknown primary site should be employed (see below), rather than relatively ineffective treatment
for a presumed insensitive primary site.
While, as mentioned above, it is not particularly helpful to label patients with a presumed primary
site, it is important to identify patients who fall into certain treatable subsets, based on either clinical
or pathologic features (see below). Specific treatment guidelines are available for these subsets. In
the remainder of patients, empiric treatment designed for cancer of unknown primary should be employed.

Management of Specific Patient Subsets
Approximately 40% of all patients with unknown primary cancer fit into a defined patient subset with specific treatment implications (Figure 1). Most of these patient groups are easily recognized after a routine clinical and pathologic evaluation.

Women With Adenocarcinoma in Axillary Lymph Nodes—Women with axillary adenopathy containing metastatic adenocarcinoma should receive treatment according to the guidelines for breast cancer. Patients in whom the axillary nodes are the only identifiable site of disease have a substantial chance for long-term survival. Positive immunoperoxidase staining for estrogen and/or progesterone receptors provides further evidence for the diagnosis of breast cancer. Even when a breast examination and mammography are unrevealing, a mastectomy will identify an occult breast primary in approximately 60% of patients.[17]

Primary treatment should include either modified radical mastectomy or axillary node dissection plus radiation therapy to the breast.[17,18] Adjuvant treatment should follow the standard guidelines for the treatment of stage II breast cancer, based on the number of lymph nodes involved, estrogen receptor status, and patient age.

Women With Peritoneal Carcinomatosis—Women with adenocarcinoma or poorly differentiated carcinoma involving the peritoneal surfaces should be treated according to the guidelines for stage III ovarian cancer. In many of these women, histologic features resemble those of ovarian cancer, including papillary or serous cystadenocarcinoma features. This syndrome has been reported in women who have historically normal ovaries or who have undergone a previous oophorectomy.[19] Serum CA-125 levels are usually elevated.

Optimal treatment for women with peritoneal carcinomatosis is identical to that currently recommended for those with advanced ovarian cancer; namely, initial laparotomy with maximal surgical cytoreduction followed by chemotherapy with paclitaxel (Taxol) and a platinum agent.[20,21] Several series report the 5-year survival rate in this patient group to be from 15% to 25%.[22-26] This syndrome has also been reported in men.[27]

Men With Osteoblastic Bone Metastases and/or Elevated PSA—All men with metastatic adenocarcinoma and elevated serum PSA levels, or positive tumor staining for PSA, should be treated for advanced prostate cancer. Responses to hormonal therapy have been documented in such patients, even when sites of metastases were atypical for prostate cancer (eg, mediastinal adenopathy, lung metastases).[28,29] Consideration should also be given to a trial of hormonal therapy in men with predominantly lytic bone metastases, even if their serum PSA level is normal.

Patients With a Single Metastatic Lesion—In some patients, only one metastatic lesion can be found, even after a complete staging evaluation. Many locations of such lesions have been reported, including lymph nodes, liver, lung, adrenal gland, brain, or bone. The possibility of a primary cancer in an unusual site, rather than a metastasis, should always be considered (eg, apocrine, eccrine, or sebaceous carcinoma presenting as skin or subcutaneous lesions; a single liver “metastasis” actually representing a hepatoma).

Treatment in this group of patients should include definitive local therapy, using surgical resection, radiation, or the two modalities combined, based on the location of the single metastasis. Many patients have a substantial disease-free interval before other metastatic lesions develop, and occasional patients enjoy long-term survival.[30,31]

The role of systemic chemotherapy, in addition to local therapy, in patients with a single metastatic lesion is undetermined. We have empirically added chemotherapy to the treatment of patients with poorly differentiated carcinomas.

Squamous Cell Cancer Involving Cervical Nodes—In most patients with squamous cell cancer presenting in cervical lymph nodes, a primary site located in the head and neck can be found after a careful endoscopic examination of the head and neck areas (ie, nasopharynx, oropharynx, hypopharynx, and larynx). Squamous cell lung cancer should be suspected in patients with involvement of low cervical or supraclavicular lymph nodes, and bronchoscopy should be considered. In approximately 15% of patients, no primary site can be identified. In these patients, treatment should follow the guidelines for locally advanced head and neck cancers.

Recently, concurrent chemotherapy plus radiation therapy has improved treatment results in patients with locally advanced head and neck cancers.[32,33] These treatment programs should also be considered in patients with cervical adenopathy and no identified primary site.

Even with local treatment modalities alone (radiation with or without radical neck dissection), 5-year survival rates of 30% to 60% have been reported in this patient group.[34-36] As in patients with
known head and neck cancers, the prognosis depends on the extent of cervical adenopathy. [37, 38]

**Squamous Cell Cancer Involving Inguinal Nodes**—In most patients presenting with squamous cell cancer in the inguinal nodes, an evaluation of the perineal structures will reveal a primary site. All patients should undergo sigmoidoscopy; female patients should have careful pelvic examinations, with colposcopy. Cystoscopy should also be considered.

If no primary site is identified, treatment should include inguinal node dissection. Patients with extensive nodal involvement should be considered for radiation therapy. About 25% of patients have prolonged survival after definitive local therapy. [39] The role of systemic therapy in this patient subset is undefined. However, with the now firmly established roles of combined-modality treatment in cancers of the cervix and anus, systemic therapy with platinum-based regimens should be considered.

**Young Men With Features of Extragonadal Germ-Cell Tumors**—Young men with poorly differentiated carcinoma involving the mediastinum or retroperitoneum should be treated according to the guidelines for extragonadal germ-cell tumors. Many of these patients will have elevated serum levels of HCG or AFP.

Molecular genetic analysis can establish a definitive diagnosis in some of these patients by identifying the pathognomonic I (12p) chromosomal abnormality. [40] The recent development of a genomic hybridization technique that can detect extra 12p material using paraffin-embedded tissue specimens may make this procedure more clinically applicable by avoiding the need to obtain fresh tissue by rebiopsy. [41] Treatment with four cycles of cisplatin (Platinol), etoposide, and bleomycin (Blenoxane) is curative in approximately 30% to 40% of these patients.

**Patients With Poorly Differentiated Neuroendocrine Carcinoma**—The diagnosis of neuroendocrine carcinoma has been improved by the routine availability of relatively specific immuno-peroxidase stains for chromogranin and synaptophysin. In some patients with neuroendocrine carcinoma, light microscopic features suggest the diagnosis; in others, the diagnosis is made solely on the basis of immunoperoxidase staining.

Patients in this group present with diverse clinical characteristics; however, these tumors share an aggressive biology and are usually sensitive to chemotherapy with platinum/etoposide combinations. In our experience, over 75% of patients had major responses, and long-term survival was achieved in 15% to 20% of patients. [42] Recently, the combination of paclitaxel, carboplatin (Paraplatin), and etoposide also showed marked activity in the treatment of these cancers. [43]

**Patients With Well-Differentiated Neuroendocrine Carcinoma**—Most patients with well-differentiated neuroendocrine carcinoma have pathologic features of carcinoid or islet cell tumors, and most present with multiple liver metastases. As opposed to poorly differentiated neuroendocrine carcinomas, these tumors are relatively indolent and relatively unresponsive to systemic chemotherapy. [44]

Management should follow the established guidelines for advanced carcinoid tumors. At times, observation is the best treatment approach, and patients with slow-growing tumors sometimes have prolonged survival with few symptoms. Treatment with somatostatin analogs, 5-FU-based chemotherapeutic regimens, or local treatment (e.g., hepatic resection, hepatic artery embolization) may also be appropriate in some instances.

**Patients With Poorly Differentiated Carcinoma**—Management of the larger, more heterogeneous group of patients with poorly differentiated carcinoma of unknown primary site is a subject of some controversy. Our experience with a large group of these patients who were treated with regimens effective in the treatment of germ-cell neoplasms, is summarized in Table 3. In this group of patients, 26% of patients had a complete response to treatment, and 16% remain continuously disease free after a minimum follow-up of 8 years. [45, 46] Some, but not all, of the patients with excellent responses had clinical features of extragonadal germ-cell tumor.

In a retrospective analysis of a large group of patients studied at the University of Texas M. D. Anderson Cancer Center, a subset of patients with poorly differentiated carcinoma achieving long-term survival could not be identified. [47] However, treatment was not uniform in these patients, and the group who received the cisplatin/etoposide-based regimens used in our series was not large. Several prognostic factors have been identified that are helpful in predicting favorable treatment outcome. These include tumor location in lymph nodes, fewer metastatic sites, younger patient age, female gender, and poorly differentiated carcinoma histology. [45, 48, 49]

**Empiric Therapy**

Approximately 60% of patients with carcinoma of unknown primary site do not belong to any of the subgroups described above. Most of these patients have adenocarcinoma. Various empiric chemotherapy regimens have been tested in this patient group. Many of these have
consisted of 5-FU–based regimens or other regimens developed for the treatment of advanced gastrointestinal cancers. Large, randomized, phase III trials have not been performed in this group of patients, and therefore, most available data regarding empiric treatment have been derived from relatively small phase II trials.

**Older Agents**—Several drugs, including 5-FU, cisplatin, oral etoposide, and mitomycin (Mutamycin), have been evaluated as single agents. All of these agents have produced response rates of 10% to 20%.[50-53]

Table 4 summarizes the results with empiric combination regimens; individual phase II trials of similar or identical combinations have been pooled, and composite efficacy results are provided.[43,54-74] Most regimens produced low response rates (20% to 33%) and similar median survival durations (4 to 7 months).

In patients with adenocarcinoma of unknown primary site, results with cisplatin-based regimens have not been superior to other regimens; however, response rates have been slightly higher. Because of their increased toxicity, cisplatin-based regimens are not considered to be standard therapy in this group of patients (as opposed to patients with poorly differentiated carcinoma of unknown primary site).[54,67-71]

**New Agents**—The availability of several new antineoplastic agents with broad clinical activity (paclitaxel, docetaxel [Taxotere], gemcitabine [Gemzar], vinorelbine [Navelbine], irinotecan [Camptosar]) offers the possibility for the development of empiric regimens with improved efficacy in patients with carcinoma of unknown primary site. Evaluation of these drugs in this group of patients has only just begun. At present, paclitaxel is the only new drug that has been evaluated as a component of empiric chemotherapy for patients with carcinoma of unknown primary site. Our first clinical experience with paclitaxel in this group of patients was in combination with carboplatin and etoposide.[43] Table 5 provides details of this regimen and summarizes the results of our initial phase II trial.

In our trial, a total of 55 patients were treated at the Sarah Cannon Cancer Center or at participating treatment sites in the Minnie Pearl Cancer Treatment Network. All 55 patients had carcinoma of unknown primary site (any histology was eligible), but patients were excluded if they fit into any recognized treatable subset. Most patients had multiple sites of metastatic disease, and a large majority had either adenocarcinoma or poorly differentiated adenocarcinoma. Patients received the combination of paclitaxel, carboplatin, and oral etoposide at 21-day intervals for a total of four to six courses.

Of the 53 patients evaluable for response, 25 (47%) had major objective responses, and 7 (13%) patients showed a complete response. Somewhat to our surprise, there was no difference in response rates when patients with adenocarcinoma were compared to those with poorly differentiated carcinoma (45% vs 48%). Median survival for the entire group was 13.4 months, with a 1-year survival rate of 58%. Survival was identical for patients with adenocarcinoma vs poorly differentiated carcinoma.

In general, this regimen was well tolerated in the outpatient setting. Grade 3 or 4 leukopenia accompanied 41% of treatment courses, but hospitalizations for treatment of neutropenia and fever were uncommon, and there were no treatment-related deaths. Other grade 3 or 4 toxicities, including peripheral neuropathy, arthralgia/myalgia, and nausea/vomiting, were uncommon. We recently updated the results of this treatment program; the group now consists of 71 patients. With longer follow-up, median survival for the entire group was 11 months; the actual 2-year survival rate was 20%, and the actual 3-year survival rate was 14%.

Therefore, this treatment regimen has produced extended survival in a minority of patients with adenocarcinoma of unknown primary site. This subset of patients with adenocarcinoma who obtain major benefit from empiric chemotherapy has not been clearly demonstrated with previous regimens.

Pavlidis et al recently reported the results of a phase II trial evaluating the combination of paclitaxel and cisplatin in patients with cancer of unknown primary site.[74] This paclitaxel-based regimen also produced a high overall response rate of 41%; in an early report, the median survival had not yet been reached but was > 8 months.

In an ongoing phase II (not yet published), randomized, multicenter European trial, the combination of paclitaxel/carboplatin/etoposide is being compared to 5-FU/leucovorin. If this randomized trial can be completed, it will definitively address the role of paclitaxel-containing therapy for carcinoma of unknown primary site.

**Ongoing or Recently Completed Clinical Trials**

At present, we are evaluating several other new drugs in the treatment of carcinoma of unknown
primary site. We have completed a trial of single-agent gemcitabine as second-line therapy. Most patients entering this trial had previously received paclitaxel and carboplatin. In this difficult-to-treat patient population, gemcitabine produced an 8% response rate, with an additional 25% of patients having stable disease or minor response with improved symptoms [75]. In an ongoing trial, we are evaluating oral topotecan (Hycamtin) as second-line treatment.

We recently completed phase II trials of first-line treatment with two different combinations: docetaxel/carboplatin and paclitaxel/carboplatin/gemcitabine. Results from these completed clinical trials should be available in the near future. Retrospectively, we have also evaluated a large group of patients with poorly differentiated carcinoma for HER-2 overexpression [76]. Overexpression of HER-2, as determined by immunoperoxidase testing, was reported in 10 (11%) of 94 patients. The efficacy of trastuzumab (Herceptin) in this patient group is a subject of further investigation.

Conclusions

Efforts to improve therapy for patients with cancer of unknown primary have been limited, due, in part, to widespread nihilism among clinicians regarding the prognosis of patients with this heterogeneous group of cancers. Improvements in pathologic diagnostic methods have resulted in a more accurate diagnosis of subsets of treatable cancers within this group. Advances in molecular genetics may further increase the proportion of patients in whom a specific diagnosis can be made, or may identify a subset of patients with tumors that are responsive to chemotherapy. Management of the large group of patients who do not fit into any currently identified treatment subset continues to be an important concern. As chemotherapy for many advanced cancers evolves, the outlook for these patients should continue to improve.

Promising results have been obtained with first-line empiric paclitaxel/carboplatin/etoposide combination chemotherapy. The regimen is well tolerated and has become one of the standard approaches to the systemic management of cancer of unknown primary. Long-term follow-up of patients treated with this regimen documents a minority of patients (14%) alive at 3 years; all of these patients had major responses to initial therapy. Additional trials of paclitaxel/carboplatin–containing regimens are in progress.

Trials evaluating other new cytotoxic agents with broad antitumor activity, including docetaxel, gemcitabine, topotecan, and irinotecan, are being conducted. If these agents demonstrate activity, further evaluation of first-line combination regimens will be indicated. Other therapeutic approaches are also under development.

The potential to improve empiric therapy for patients with carcinoma of unknown primary site is promising. A broader scope of clinical trials in these patients is warranted.

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