Optimal therapeutic management of patients with distinct clinicopathological cancer of unknown primary subsets

N. Pavlidis*

Department of Medical Oncology, School of Medicine, University of Ioannina, Ioannina, Greece

Cancer of unknown primary sites (CUP) is a compilation of various malignant entities—the majority of which behave aggressively and carry poor prognosis. CUP is classified into two different clinicopathological groups: the unfavourable (poor-prognosis) and the favourable (good-prognosis) group. Patients with favourable subsets are treated relevant to the hidden primary tumour chemotherapy regimens and/or radiotherapy. These patients exhibit better responses and prolonged survival. On the other hand, patients of unfavourable subsets are treated with various chemotherapy combinations of platinum- or taxane-containing regimens. Unfortunately, responses and overall survival in this group of CUP patient are not very promising. Several independent prognostic factors have been associated with survival of CUP patients. Since CUP is not an unknown disease, emerging therapeutic innovations are warranted.

Key words: cancer of unknown primary, clinicopathological subsets, treatment

introduction

Cancer of unknown primary (CUP) is a heterogenous clinical entity and accounts for 3%–5% of all cancers, representing one of the 10 most common malignancies. The median age is ~60 years and males are more commonly affected than females. Both diagnostic and therapeutic approaches remain a dilemma for practising oncologists. CUP is defined as those patients in whom detailed work-up including blood and imaging tests as well as extensive and specific immunohistochemistry fails to detect the primary site.

The diagnostic work-up for the identification of the primary site includes: (i) pathology with extensive immunohistochemistry; (ii) imaging radiology (conventional X-rays, CT scans, PCT scans); (iii) endoscopies and (iv) serum markers.

Histopathologically, CUP is divided into the following subtypes: (i) adenocarcinoma well-to-moderately differentiated (50%); (ii) undifferentiated or poorly differentiated adenocarcinoma (30%); (iii) squamous cell carcinomas (15%) and (iv) undifferentiated neoplasms (5%) including neuroendocrine tumours, lymphomas, germ-cell tumours, melanomas, sarcomas or embryonal carcinomas.

CUP shares a unique natural history consisting of early dissemination, clinical absence of primary site, an aggressive disease most of the times and an unpredictable metastatic pattern [1, 2].

Although multigene profiling platforms or micro-RNAs technology can precisely identify the tissue of origin of primary site by 75%–90%, this molecular testing is not used in daily practice [3].

CUP is classified into two prognostic groups: (i) poor prognosis or unfavourable subsets (80%) and (ii) the good prognosis or favourable subsets (20%).

The unfavourable groups consist of: (i) adenocarcinoma metastatic to the liver or other organs; (ii) non-papillary malignant ascites (adenocarcinoma); (iii) multiple cerebral metastases (adenocarcinoma or squamous cell carcinoma); (iv) multiple lung/pleural metastases (adenocarcinoma); and (v) multiple metastatic bone lesions (adenocarcinoma).

In the favourable groups, the following CUP subsets are included: (i) women with papillary adenocarcinoma of peritoneal cavity; (ii) women with adenocarcinoma involving only axillary lymph nodes; (iii) poorly differentiated carcinoma with midline distribution; (iv) squamous cell carcinoma involving cervical lymph nodes; (v) adenocarcinoma with a colon cancer profile (CK20+, CK7−, CDX2+); (vi) poorly differentiated neuroendocrine carcinomas; (vii) men with blastic bone metastases and elevated prostate specific antigen (PSA) (adenocarcinoma); (viii) patients with limited disease (isolated inguinal adenopathy from squamous carcinoma or a single, small, potentially resectable tumour) (Table 1) [1, 2].

treatment of unfavourable subsets

The most common subset among the poor prognosis group is that of metastatic liver disease of adenocarcinoma histology. All patients who belong to this group are mainly treated with platinum- and/or taxane-containing regimens. Almost 400 patients with metastatic adenocarcinoma to the liver treated with the above combinations achieved a response rate of <20%
and a median survival of ~7 months [4]. More recent data claim more favourable responses and longer survival; however, these studies are based in a better patient selection.

Various phase II or III randomised studies failed to demonstrate survival benefit [5]. A meta-analysis carried out with more than 800 unfavourable CUP patients has shown that none of the chemotherapy regimens used could prolong survival (Tables 2 and 3) [6].

Nevertheless, patients of relatively young age and of good performance status should be considered candidates for chemotherapy. On the contrary, in older patients with poor performance status, best supportive care should be recommended [7].

Second-line chemotherapy using various combinations including fluorouracil, leukovorin, gemcitabine, irinotecan or docetaxel demonstrated low responses and no survival advantages [8–11]. In one recent study, the combination of oxaliplatin and capecitabine showed 19% response rate and an overall survival of 9.7 months [12].

Targeted treatment with bevacizumab and erlotinib was studied as second-line treatment in a phase II trial with 51 patients. Eight percent achieved partial response and 59% stable disease, and median overall survival was 8–9 months [13].

treatment of favourable subsets

women with papillary adenocarcinoma of the peritoneal cavity (‘primary peritoneal carcinomatosis’)

The median age is 55–65 years and the clinical presentation is similar to ovarian cancer with increased serum levels of CA 125 in almost 80% of the cases. Histopathology is compatible with papillary serous adenocarcinoma. These patients are treated as stage III and IV ovarian cancer patients with responses up to 80% (30–40% complete responders) and a median survival of 36 months [14].

women with isolated adenocarcinoma involving the axillary nodes

These women are behaving clinically as stage II breast cancer patients. The median age is 52 years, mostly postmenopausal females. Almost half of patients have N2–3 disease and the majority are diagnosed as ductal carcinoma.

These patients should be treated with mastectomy or breast irradiation, axillary clearance and adjuvant systemic therapy (chemotherapy, hormonal therapy or trastuzumab) according to the indication [15].

poorly differentiated carcinoma with midline distribution

It is more common in males below 50 years old, involves primarily mediastinal or retroperitoneal lymph nodes and shares histological features of extragonadal germ-cell tumours.

These cases should be managed as poor-prognosis germ-cell tumours with platinum-containing chemotherapy. Despite its germ-cell characteristics, the median response rate is ~45%, with only 20% complete responders and a median survival of 1 year [16].

squamous cell carcinoma involving cervical lymph nodes

The median age is ~60 years and it is predominantly a male disease. Diagnostically, PET/CT shows high sensitivity in detecting the primary site. The recommended treatment is similar to locally advanced carcinoma of the head and neck,
including radical neck dissection, external beam irradiation to the pharyngeal axis and bilateral neck and concurrent chemoradiotherapy mainly for N2/N3 disease. Locoregional management offers long-term disease control in 50%–60% of patients [17].

neuroendocrine carcinomas of unknown origin
Most of these patients are diagnosed with poorly differentiated large-cell neuroendocrine tumours (>75%) and the rest with low grade. Poorly differentiated neuroendocrine CUP patients are treated with platinum-based or platinum-taxane-containing regimens. The overall response rate is ~50%–55% (with up to 20% complete responders) and median survival is 15.5 months. Around 10%–15% of patients might enjoy long-term survival. Well-differentiated histology patients are treated with somatostatin analogues, streptozotocin with or without 5FU, sunitinib, everolimus [18].

adenocarcinoma with colon-cancer profile
This is a recently described favourable subset. These cases are presented with multiple metastases (mainly liver secondaries) which are immunohistochemically characterised as CK20+, CK7− and CDX-2+. They respond to colon cancer-specific combination chemotherapy regimens and exhibit a median survival of 20–24 months [19].

men with blastic bone metastases from an adenocarcinoma and an elevated serum PSA
These patients should be considered as having metastatic prostate cancer. They present with secondary bone lesions, elevated serum PSA and immunohistochemical staining positive for PSA. They should be managed with endocrine treatment [1, 2].

patients with limited disease
These patients are quite rare and present either with isolated inguinal lymph nodal metastatic squamous cell carcinoma or with a single metastatic lesion. They should be treated with local dissection with or without local radiation therapy. They exhibit long disease-free survival [1, 2].

prognostic factors
Several independent prognostic factors are associated with survival in CUP patients.
Among them are male sex, poor performance status, high number of metastatic sites, unfavourable histopathological subsets, presence of liver metastases, elevated alkaline phosphatase, elevated serum lactate dehydrogenase, low serum albumin levels and lymphopenia [20, 21].

disclosure
The authors have declared no conflicts of interest.

references


