Carcinoma of Unknown Primary (CUP): Diagnosis and Treatment

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Epidemiology

Incidence and mortality

The definition of carcinoma of unknown primary (CUP) includes patients who have histologically confirmed metastatic cancer in whom a detailed medical history, complete physical examination including pelvic and rectal examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, computed tomography (CT) of the abdomen and pelvis and, in certain cases, mammography fail to identify the primary site. Carcinoma of unknown primary (CUP) is the seventh to eighth most frequently occurring cancer in the world and the fourth commonest cause of cancer death in both males and females. CUP accounts for some 2.3–4.2% of cancer in both sexes.

The annual age-adjusted incidence per 100,000 population in USA is 7–12 cases, in Australia 18–19 cases and in the Netherlands 5.3–6.7 cases. The median age for occurrence is around 60 years and CUP is marginally more frequent in males.

Aetiology and risk factors

In this heterogenous group of tumours, most of which follow an aggressive biological and clinical course, there are no obvious aetiological or risk factors that contribute to the pathogenesis of this syndrome.

Early diagnosis

Early detection of CUP is not possible. Therefore, no current screening programmes are available.

Pathology and biology

Almost 50% of patients with CUP will be diagnosed with metastatic adenocarcinoma of well to moderate differentiation, 30% with undifferentiated or poorly differentiated carcinomas, 15% with squamous cell carcinomas and the remaining 5% will have undifferentiated neoplasms.

Immunohistopathological studies can be utilised to further characterize the undifferentiated neoplasms, poorly differentiated carcinomas, neuroendocrine tumours, lymphomas, germ cell tumours, melanomas, sarcomas and embryonal malignancies.

In children, embryonal malignancies make up the majority of the rare cases of disseminated malignancies without an identified primary tumour.

Biology

CUP is a heterogeneous group of tumours. There is no evidence regarding whether CUP carries a distinct biological entity involving specific genetic and phenotypic alterations.

The issue has not been extensively investigated on a molecular basis, and the limited information available is still controversial and inconclusive.

In general, CUP follows an aggressive biological and clinical behaviour.

Chromosomal and molecular abnormalities

Chromosomal abnormalities have been detected in the short arm of chromosome 1 including deletion of 1p, translocations with a breakpoint at 1p, isochromosome 1q and evidence for gene amplification. Identical results have also been reported in other advanced malignancies. Similar chromosomal abnormalities have been found in the short arm of chromosome 12. The isochromosome i(12)p or a deletion in 12p – a germ cell chromosomal marker – was observed in 25% of patients with poorly differentiated carcinoma and predominant lymph nodal disease.

Chromosomal instability (anenploidy) was found in 70% of patients with metastatic adenocarcinoma or undifferentiated carcinoma.

In one study, overexpression of c-myc, ras and c-erB-B2, as demonstrated by immunohistochemistry, was reported in 96%, 92% and 65% of cases, respectively. However in another study c-erB-B2 expression was found in 11% of patients with poorly differentiated carcinomas and. Additionally, using immunohistochemistry bcl-2 and p53 were overexpressed in 40% and 53% of cases, respectively, whereas using PCR only 26% of patients expressed p53. Furthermore, the incidence of p53 mutations was 26% of the cases studied. Strong EGFR expression was observed in 12% of patients, but no evidence of EGFR exon 18, 19, and 21 amplification was detected. No differences in angiogenesis, as measured by microvessel density, were detected between CUP patients with liver metastases and those with hepatic secondaries from known primaries. Strong expression of VEGF and stromal TSP-1 was seen in 83% and 20%, respectively. MMP-2, MMP-9 and TIMP-1 are widely expressed in CUP patients, suggesting an essential role of proteolysis in these tumors.

Diagnosis

Diagnostic evaluation for the identification of primary site and staging

Despite extensive work-up, less than 20% of patients with CUP have a primary site of their cancer identified antemortem. Autopsy studies have reported that 70% of cases remained undiagnosed.

Diagnostic pathology

An adequate sample of tumour tissue is essential for carrying out light microscopy examinations, immunohistochemical investigations, evaluating other markers or receptors as well as performing more specific investigations such as electron microscopy or genetic/molecular studies.

Light microscopy can only characterize cell morphology and tumour differentiation.

Immunohistochemical studies are of paramount importance. Several cell components can be identified by the immunoperoxidase technique using a series of monoclonal or polyclonal antibodies to enzymes, structural tissue components (i.e. cytokeratins), hormonal receptors, hormones, oncofetal antigens or other substances. For metastatic adenocarcinomas a simplified diagnostic panel of only 10 markers has been developed. These markers are: CA 125, CDX2, cytoceratins 7 and 20, estrogen receptor, gross cystic disease fluid protein 15, lysozyme, mesothelin, PSA and thyroid transcription factor 1

Electron microscopy should be considered in the evaluation of poorly differentiated neoplasms in young patients, particularly when immunnoperoxidase stains are inconclusive.

Cytogenetic analysis could be useful in the evaluation of young patients with poorly differentiated carcinomas or undifferentiated neoplasms potentially responsive to chemotherapy, i.e. identification of isochromosome i(12p) in poorly differentiated carcinoma with lymph nodal midline distribution, of translocation t[11; 22] [q24; q12] in peripheral neuroectodermal tumour and Ewing's sarcoma, of t[8; 14] [q24; q32] in non-Hodgkins lymphomas, of t[3; 13] in alveolar rhabdomyosarcoma or of 3p deletion in small cell lung carcinoma and.

Diagnostic molecular technology

Identification of primary site by multiple gene expression profiling (DNA microarrays platforms) carries a relatively high specificity and sensitivity, however its potential therapeutic or prognostic benefit remains questionable.

Diagnostic radiology

In terms of conventional radiology, a routine chest radiograph is part of the initial evaluation of the patient with CUP.

CT of the abdomen and pelvis results in the detection of a primary site for the cancer in 30–35% of patients. CT of the chest has not been adequately studied. CT scans can also be helpful in evaluating the stage of the disease.

Mammography has been recommended for female patients with metastatic adenocarcinoma involving axillary lymph nodes.

Magnetic resonance imaging was found to be very sensitive for the detection of mammographically occult breast cancer.

FDG-PET scans are a valuable modern imaging technique for patients with CUP, particularly for patients with squamous pathology involving the cervical lymph nodes.

Diagnostic endoscopy

Endoscopic studies should always be directed towards investigating specific symptoms or signs. For example, patients with pulmonary symptoms and/or indications for imaging should be offered fiberoptic bronchoscopy, or patients with abdominal symptoms or occult blood in the stool should be investigated with gastrointestinal endoscopies.

Diagnostic value of serum tumour markers

Serum β-chorionic gonadotropin (b-HCG), α-fetoprotein (AFP) and prostate specific antigen (PSA) should be requested for male patients with CUP, in order to exclude treatable extragonadal germ cell tumours and metastatic prostate cancer.

High levels of serum thyroglobulin in CUP patients with bone metastases is indicative of an occult thyroid cancer. In certain sub-sets, such as those with isolated axillary nodal metastatic disease and in peritoneal papillary adenocarcinomatosis, serum CA 15-3 and CA 125 could be of some help.

Staging

Clinicopathological sub-sets

It is very important to classify CUP patients into established clinicopathological sub-sets in order to guide diagnostic approaches and to be able to offer optimal therapeutic management. The classification of the different clinicopathological entities is shown in table1.

Prognosis

Prognostic and predictive factors

Median survival in CUP patients enrolled in clinical studies ranges from 6 to 10 months, but in an unselected CUP population outside a clinical trial, life expectancy is only 2–3 months.

The prognostic and predictive factors examined in two available studies include age, gender, performance status, weight loss, histopathology, tumour burden, tumour location, number of metastatic sites and serum markers. The factors characterized as significant were certain histopathological sub-sets (poorly differentiated carcinoma, squamous cell carcinoma, and neuroendocrine carcinoma), number of metastatic lesions (≤2), female sex, performance status, weight loss and various serum markers (alkaline phosphatase, LDH, and CEA). The detection of these prognostic and predictive factors helped to distinguish the favourable from the unfavourable groups of CUP patients.

Treatment

Overall strategy

Treatment recommendation for CUP patients is based on a type 3 level of evidence and available treatment options are considered as suitable for individual clinical use or investigational. For adequate therapeutic guidance CUP entities should be categorized into favourable or unfavourable sub-sets. Some favourable sub-sets require specific treatment approaches and have the potential for an excellent treatment outcome. The favourable and unfavourable sub-sets of CUP are illustrated below.

Favourable sub-sets

1. Poorly differentiated carcinoma with midline distribution (extragonadal germ cell syndrome).

2. Women with papillary adenocarcinoma of the peritoneal cavity.
3. Women with adenocarcinoma involving only axillary lymph nodes.
4. Squamous cell carcinoma involving cervical lymph nodes.
5. Isolated inguinal adenopathy (squamous carcinoma).
6. Poorly differentiated neuroendocrine carcinomas.
7. Men with blastic bone metastases and elevated PSA (adenocarcinoma).
8. Patients with a single, small, and potentially resectable tumour.

Unfavourable sub-sets

1. Adenocarcinoma metastatic to the liver or other organs.
2. Non-papillary malignant ascites (adenocarcinoma).
3. Multiple cerebral metastases (adeno or squamous carcinoma).
4. Multiple lung/pleural metastases (adenocarcinoma).
5. Multiple metastatic bone disease (adenocarcinoma).

Treatment of favourable groups

Poorly differentiated carcinoma with midline distribution (extragonadal germ cell syndrome)

This sub-set of CUP should be managed in a manner similar to poor prognosis germ cell tumours with platinum-based combination chemotherapy, on a type 3 level of evidence. More than 50% response has been reported, with 15–25% complete responders and 10–15% long-term disease-free survivors.

Women with papillary adenocarcinoma of peritoneal cavity

These patients should optimally be treated as FIGO stage III ovarian cancer with aggressive surgical cytoreduction followed by platinum-based postoperative chemotherapy, on a type 3 level of evidence. Survival is identical to FIGO stage III ovarian cancer patients.

Women with adenocarcinoma involving only axillary lymph nodes

In these patients, locoregional treatment with or without systemic therapy is suggested. The management is similar to that of stage II or III breast cancer. In patients with N1 disease (mobile nodes) axillary clearance followed is either a simple mastectomy or breast radiotherapy is recommended. In premenopausal women with positive oestrogen receptors, adjuvant chemotherapy followed by tamoxifen administration is recommended. For postmenopausal patients with positive oestrogen receptors tamoxifen is still recommended. No data are available concerning adjuvant chemotherapy in these patients. In patients with N2 disease (fixed nodes), preoperative neoadjuvant chemotherapy is suggested following the guidelines for stage III breast cancer. However, in non-responding tumours or in elderly patients, radical radiotherapy should be the treatment of choice. Oestrogen receptor positive patients should continue on tamoxifen treatment. All the above data are on a type 3 level of evidence.

The reported 5- and 10-year overall survival rates are 75% and 60%, respectively.

Squamous cell carcinoma involving cervical lymph nodes

These patients should be treated with locoregional management according to the guidelines for locally advanced head and neck cancer. The 5-year survival rates range from 35 to 50% with documented long-term disease-free survivors, on a type 3 level of evidence.

Surgery alone is inferior and can be recommended only in selected patients, particularly those with pN1 neck disease with no extracapsular extension.

Radiotherapy to the ipsilateral cervical nodes alone is still inferior to extensive irradiation to both sides of the neck and the mucosa in the entire pharyngeal axis and larynx. Whether such an intensive irradiation prolongs survival is still uncertain.

Although the role of systemic chemotherapy remains undefined, concurrent chemoradiotherapy seems to be beneficial particularly in patients with an N2 or N3 lymph node disease.

Isolated inguinal lymphadenopathy from squamous cell carcinoma

Inguinal node dissection, with or without local radiotherapy, is the recommended treatment for this sub-set of patients on a type R basis. Long-term survivors have been reported.

Poorly differentiated neuroendocrine carcinomas

This group of CUP patients should be treated with platinum-based or paclitaxel/carboplatin-based chemotherapy on a type 3 level of evidence. The reported response rates are as high as 50–70% with 25% complete responders and 10–15% long-term survivors.

Men with blastic bone metastases and elevated PSA from an adenocarcinoma

This rare sub-set of CUP patients, although still debatable, should be considered as having metastatic prostate cancer and endocrine treatment is recommended as the initial therapy on a type R basis.

CUP patients with a single small metastasis

Local treatment with either resection and/or radiotherapy should be recommended on a type R basis. A considerable number of these patients enjoy palliative benefit and some of them a long disease-free survival.

Treatment of unfavourable groups

No chemotherapy regimen has been found convincingly effective for the majority of CUP patients presenting with disseminated bone, liver or multi-organ metastases of adenocarcinoma, Despite some evidence of response, median survival is still in the range of 8–9 months, although some slight differences in 1, 2 or 3 years survival have been reported. Chemotherapy regimens used include platinum or taxane/platinum combinations, on a type 3 level of evidence.

Randomized studies have shown similar activity between platinum combined with gemcitabine or irinotecan as well as between platinum- and taxane-based chemotherapy, on a type 2 level of evidence. Only investigational treatment options apply to these patients. Alternatively, low toxicity chemotherapy of palliative intent or best supportive care should be considered.

Second-line chemotherapy

Second-line chemotherapy with various regimens in patients who have failed platinum-based treatment has been reported to be ineffective, on a type 3 level of evidence. Early data with targeted treatment (bevacizumab and erlotinib) showed substantial activity and acceptable tolerance on a type 3 level of evidence.

Late sequelae

Late sequelae related to surgery, radiation therapy and chemotherapy

Clinically significant long-term sequelae related to surgery in specific CUP sub-sets, i.e. in women with adenocarcinoma involving axillary lymph nodes or in women with papillary adenocarcinoma of peritoneal cavity or in patients with squamous cell carcinoma involving cervical lymph nodes, are no different from the relevant surgical late complications of patients with known primary breast, ovarian or head-neck cancers of similar clinical stages. Clinically long-term sequelae related to radiation therapy in women with adenocarcinoma involving axillary lymph nodes or in patients with squamous cell carcinoma involving cervical lymph nodes are similar to those of known primary breast and head-neck cancers. In a majority of patients late sequelae attributable to chemotherapy do not represent a clinical problem since median survival is no longer than 1 year. In the minority of patients with long-term survival late toxicities are similar to those seen in patients treated with platinum- and/or taxane-based chemotherapy.

Follow-up

The short life expectancy of CUP patients leaves little room for developing guideline recommendations for a follow-up strategy. As a general rule, after completion of treatment, patients in sub-sets with a poor prognosis should attend outpatient clinics upon need, but patients with a favourable CUP sub-set diagnosis should be seen on a regular basis similar to that followed for the respective solid tumour, such as germ-line tumours for patients with middle line distribution, ovarian cancer for carcinomatosis peritonei in women and breast cancer for patients with axillary nodal metastases.

Organ	Histology
Liver (mainly) and/or other organs	AdenoCa moderately or poorly differentiated
Lymph nodes	
Mediastinal–retroperitoneal (midline distribution)	Undifferentiated or poorly differentiated Ca
Axillary	AdenoCa well to poorly differentiated
Cervical	Squamous cell Ca
Inguinal	Undifferentiated Ca, squamous, mixed squamous/adenoCa
Peritoneal cavity	
Peritoneal adenocarcinomatosis in females	Papillary or serous adenoCa (±psammoma bodies)
Malignant ascites of other unknown origin	Mucin-producing adenoCa moderately or poorly differentiated (±signet ring cells)
Lungs	
Pulmonary metastases	AdenoCa of various differentiations
Pleural effusions	AdenoCa moderately or poorly differentiated
Bones (solitary or multiple)	AdenoCa of various differentiations
Brain (solitary or multiple)	AdenoCa of various differentiations or squamous cell Ca
Neuroendrocrine tumours	Poorly differentiated Ca with neuroendocrine features (mainly), low-grade neuroendocrine Cas, small cell anaplastic Cas
Malignant melanoma	Undifferentiated neoplasm with melanoma features

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