Article published online: 2021-06-23

Review Article

Cancer of Unknown Primary: Opportunities and Challenges

Abstract

Cancer of unknown primary (CUP) is defined as histologically proven metastatic tumors whose primary site cannot be identified during pretreatment evaluation. Among all malignancies, 3%–5% remained as CUP even after the extensive radiological and pathological workup. Immunohistochemistry and molecular gene expression tumor profiling are being utilized to predict the tissue of origin. Unfortunately, the survival of these patients remains poor (6–9 months) except in 20% of patients who belong to a favorable subset (12–36 months). There is a need to understand the basic biology and to identify the molecular pathways which can be targeted with small molecules. This article reviews our current approach as well as treatment evolution occurred in the past three decades.

Keywords: *Cancer of unknown primary, empirical chemotherapy, immunohistochemistry, molecular tumor profiling*

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Introduction

Cancer of unknown primary (CUP) is defined as histologically proven metastatic tumors whose primary site cannot be identified during pretreatment evaluation.[1] Pretreatment evaluation usually consists of detailed clinical history, examination, and various imaging modalities. In the literature, apart from CUP, others terminologies are also being used to describe this entity such as "occult primary tumors" or malignancy of unknown origin. Among all malignancies, 3%–5% remained as CUP even after the extensive radiological and pathological workup.[2] The three most important characteristics of CUP are early dissemination, aggressiveness, and unpredictable metastatic pattern. Immunohistochemistry (IHC) and molecular gene expression tumor profiling (MTP) are being utilized, earlier being more commonly used, to predict the tissue of origin (TOO). Unfortunately, the survival of these patients remains poor (6–9 months) except in 20% of patients who belong to a favorable subset (12–36 months). There is a need to understand the basic biology and to identify the molecular pathways which can be targeted with small molecules.

Pathological Evaluation

Histological examination with hematoxylin and eosin (H and E) staining is the first step for initial evaluation. It provides the important classification system on which further evaluation is based. Based on H and E examination, CUP patients can be divided into five categories.

Poorly differentiated neoplasm

when pathologist cannot assign the general category such as carcinoma, lymphoma, sarcoma, or melanoma, the term commonly used is poorly differentiated neoplasm (PDN). Five percentage of all CUP patients is diagnosed as PDN. Since most of these tumors are responsive to chemotherapy, every effort should be made to make a correct diagnosis. Two-third of patients ultimately found to have lymphoma, a highly treatable neoplasm with combination chemotherapy with or without rituximab.[3] Remaining tumor includes neuroendocrine carcinoma, sarcoma, and rarely melanoma. MTP should be used if TOO cannot be predicted by IHC.

Poorly differentiated carcinoma

Poorly differentiated carcinoma (PDC) forms second largest group of CUP patients, comprising 29% of the patients. One-third of patients can have associated featured of adenocarcinoma. Responsive tumors are occasionally identified. Additional IHC markers are used to identify 3% of patients who are mistaken for carcinoma.

How to cite this article: Rajeev LK, Asati V, Lokesh KN, Rudresh AH, Babu S, Jacob LA, *et al.* Cancer of unknown primary: Opportunities and challenges. Indian J Med Paediatr Oncol 2018;39:219-26.

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Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_91_17

Quick Response Code:

In reality, they are lymphoma, sarcoma, or melanoma. Neuroendocrine carcinoma is detected in another 1% of patients.

Adenocarcinoma

Adenocarcinoma forms the largest group of CUP patients, comprising 60% of the patients, usually presents as metastatic tumor at multiple sites such as lymph nodes, liver, lung, and bone. Morphologically, they are well differentiated to moderately differentiated. To predict, the TOO based on morphology is difficult, as they share common morphology like the formation of glandular pattern by neoplastic cells, and hence, IHC ± MTP plays an important role.[4]

Squamous cell carcinoma

Squamous cell carcinoma (SCC) forms 5% of all CUP patients. They mostly present as unilateral or bilateral cervical lymphadenopathy. Other site being inguinal lymph nodes and rarely axillary lymph nodes. IHC is rarely useful. More than 80% of patients belong to favorable subset, and hence, can be managed effectively.

Neuroendocrine tumors

Remaining 1% of patients of CUP belong to this category. Based on H and E examination, these tumors can be divided into low grade or high grade. The third subgroup which cannot be identified by H and E examination, due to lack of neuroendocrine features, requires IHC ± MTP.[5]

Immunohistochemistry

IHC staining is the most commonly used, widely available specialized technique for the classification of neoplasm and accurately predicting the TOO. In the past two decades, there is a tremendous improvement in the availability of newer and specific IHC markers.[6] Most markers are directed at normal cellular proteins that are retained during the malignant transformation. Initial markers depend on the age, sex, clinical presentation, site involvement and most important basic category as assigned by H and E examination. Most pathologists use CK7 and CK20 as initial IHC markers while some prefer to use thyroid transcription factor-1 (TTF-1) and CDX-2 along with CK7 and CK20.[7] When the tumor belongs to the category of PDN, the first step is to assign the general category such as carcinoma, lymphoma, sarcoma melanoma, or mesothelial tumors [Table 1]. Based on the result of CK7 and CK20, the further IHC markers can be used [Table 2].

IHC result may lead to addition diagnostic procedures to detect the primary tumor. Technical expertise is required while performing IHC and interpreting the result is subjective and requires experienced pathologist. IHC markers are not specific (except prostate-specific antigen [PSA] staining), and there can be significant overlap [Table 3].[4,8] Sometime, pathologist may suggest more than one sites of primary. When IHC is inconclusive, MTP, cytogenetics, or sometime electron microscopy helps in predicting TOO.

Table 1: Use of immunohistochemistry markers to assess cell lineage

Markers	Cell lineage
Pan-keratin (AE1/AE3, CAM 5.2)	Carcinoma
CK5/6, p63/p40	SCC
S100, sox10	Melanoma
LCA ± CD20	Lymphoma
OCT3/4 ± SALL4	Germ cell tumor
WT1, calretinin, mesothelin	Mesothelial tumor

SCC – Squamous cell carcinoma; LCA – Leukocyte common antigen

Molecular Tumor Profiling

During the process of malignant transformation, cancer cell retains some of the functional characteristics which are specific to their TOO and can be easily identified by gene expression profiles (GEP).[9] The molecular basis of MTP is the identification of these genes responsible for the synthesis of proteins required for specific normal cellular functions or relatively specific cytoplasmic microRNA. In simple words, the MTP is not designed to detect cancer-specific molecular abnormality rather it detects the genes in relation to cell lineage. Two MTP assays are commercially available as follows.

1. 92-gene reverse transcription polymerase chain reaction mRNA assay (Cancer TYPE ID; bioTheranostics, Inc.)[9]
2. Microarray methodology to measure tissue-specific microRNAs (Cancer of Origin Test, Rosetta Genomics).[10]

However, before we start using MTP in our clinical practice, the following three questions need to be addressed:

1. Are they accurate in diagnosing known primary cancers?
2. Are they accurate in diagnosing the TOO in CUP?
3. Are the outcomes of CUP patients improved by site-specific therapies directed by MTP diagnoses?

The study by Monzon *et al*.[11] was the first adequately sized, blinded, multicenter validation study of 1,550-GEP for determination of tumor TOO. Frozen specimens of 547 patients of known primary were processed using oligonucleotide microarrays. The study found the overall sensitivity of 87.8% and overall specificity of 99.4% indicating high accuracy in predicting the TOO in patients with known primary. Many studies validated MTP in patients with known primary tumors with an accuracy of approximately 90%.[12-14] Another important advantage of MTP is the requirement of lesser tissue, and accuracy is well maintained irrespective of specimen type whether the specimen is fine-needle aspiration/cytology cell blocks, core biopsies, or small excisions.[15]

Table 2: Basic immunohistochemistry markers workup for cancer of unknown primary patients

Primary markers	Possible primary sites/tumor	Additional markers
CK7− CK20+	Colorectal and Merkel cell carcinoma	CEA and CDX-2
CK7+ CK20−	Lung, breast, thyroid, uterus, cervix, pancreas, and cholangiocarcinoma	TTF-1, ER, PR, GCDFP-15 and CK19
CK7+ CK20+	Urinary bladder, ovary, pancreas, and cholangiocarcinoma	Urothelin and WT-1
CK7− CK20−	HCC, RCC, prostate, and SCC	Hep Par-1 and PSA

SCC – Squamous cell carcinoma; HCC – Hepatocellular carcinoma; RCC – Renal cell carcinoma; CEA – Carcinoembryonic antigen; TTF-1 – Thyroid transcription factor-1; GCDFP-15 – Gross cystic fluid protein 15; PSA – Prostate-specific antigen; ER – Estrogen receptor; PR – Progesterone receptor; CK – Cytokeratin; CDX – Caudal-type homeobox transcriptional factor 2

Table 3: Immunohistochemical staining in differential diagnosis of cancer of unknown primary patients

Tumor type	Immunohistochemical markers
Gastrointestinal stromal tumor	CD117+, CD34+, DOG1+
Mesothelioma	Calretinin+, CK5/6+, WT1+, Mesothelin+
Colorectal cancer	CK7−, CK20+, CDX-2+
Lung: Adenocarcinoma	CK7+, CK20-, TTF-1+, napsin A+
Lung: Squamous	CK7+, CK20-, p63+
Breast	CK7+, ER+, PR+, Her2/neu+, GATA3+, GCDFP−15+, mammaglobin+
Ovary	CK7+, ER+, WT1+, PAX8+, mesothelin+
Prostate	PSA+, CK7−, CK20−
Pancreas	CK7+, Ca19.9+, mesothelin+
RCC	RCC+, PAX8+, CD10+
Hepatocellular cancer	Hepar1+, CD10+

GCDFP-15 – Gross cystic fluid protein 15; PSA – Prostate-specific antigen; ER – Estrogen receptor; PR – Progesterone receptor; TTF-1 – Thyroid transcription factor-1; RCC – Renal cell carcinoma

Regarding the second question, we can assume that MTP will predict correct TOO as predicted in patients with known primary. However, in this era of evidence-based medicine, we need preferably direct or at least indirect evidence. Direct evidence for accurately assessing the TOO can be accumulated if patients develop the same primary tumor as predicted by MTP, during their lifetime. Only 5% of CUP patients develop the primary tumor during their lifetime, and hence, collecting data prospectively is difficult and unrealistic. In a retrospective, multi-institutional study by Greco *et al*.,[16] evaluated 501 CUP patients treated between 2000 and 2008. Thirty-eight of 501 patients (7.6%) developed primary tumor during their lifetime. MTP was performed on the tissue of 20 of these 38 patients. In 15 patients (75%), the predictions were correct (95% confidence interval, 60%–85%).

The indirect evidence for accurately predicting the TOO by MTP can be assessed by comparing with IHC in patients with known primary tumor. Handorf *et al*. prospectively conducted, blinded multicenter study directly comparing the diagnostic accuracy of GEP and IHC for primary site identification in metastatic tumors in 157 patients of known primary tumor.[17] GEP accurately identified 89% of specimens, whereas IHC identify 83% specimen accurately (P = 0.013). In 33 PDC specimens, GEP accuracy exceeded that of IHC (91% to 71%, P = 0.023). Moreover, when the pathologist was able to give a diagnosis with a single round of IHC markers, there was 90% correlation between IHC and GEP. When the second round of IHC marker was required, GEP predicts the TOO more correctly (83% vs. 67%, $P < 0.001$).

To summarize, MTP predicts the TOO in a majority (about 95%) of patients with an accuracy of 75%–80%. The correlation between IHC and MTP diagnoses is good when IHC predicts a specific TOO, and hence, in patients with diagnostic IHC, MTP is not necessary. However, when IHC is inconclusive, MTP provides valuable additional diagnostic information.

The Role of Fluorine-18 Fluorodeoxyglucose Positron-emission Tomography/Computed Tomography

As per the available literature, the elective use of positron-emission tomography/computed tomography (PET/CT) is limited in patients with SCC who present with cervical lymph nodes involvement, especially upper and middle cervical lymph nodes, when routine investigations including triple endoscopy failed to detect the primary tumors.[18-20] In most of the patients, primary remains occult in the head and neck region. PET/CT help to detect the possible primary site in 24.5% of tumors that remain occult after conventional work up. The combined analysis of 16 studies, published between 1994 and 2003, by Rusthoven *et al.*, PET/CT leads to detection of previously unrecognized metastases in 27.1% of patients (regional - 15.9%; distant - 11.2%) definitely changing treatment approach in these patients.[19]

We do not have much data regarding the use of PET/CT in patients with extracervical carcinoma. NCCN guideline recommends against the use routine of PET/CT in these patients unless definitive therapy is planned. A prospective study by Moller *et al*. compared PET/CT and CT as diagnostic tools to identify the primary tumor site in 136 newly diagnosed extracervical CUP patients.[21] PET/CT when compared with CT, the specificity, sensitivity, and diagnostic accuracy were 71%, 57.6%, and 64.4%, versus 60.9%, 65.2%, and 63%, respectively. There was no statistical difference between two imaging modalities.

Serum Tumor Markers

Serum tumor markers are more useful for response evaluation and follow-up rather than in making diagnosis. There are few exceptions. Serum PSA is prostate-specific markers and very high serum level, with the presence of osteoblastic bone metastasis can be taken as diagnostic of adenocarcinoma prostate. Serum alpha-fetoprotein (AFP) level is an important diagnostic criterion for the diagnosis of hepatocellular carcinoma with triple-contrast CT scan. In young patients presenting with midline tumor, testicular mass, or multiple pulmonary metastasis with increased serum level of AFP with or without beta-human chorionic gonadotropin (HCG), germ cell tumor should be taken as a diagnosis until prove otherwise.[22] CA 125, CA19.9, and carcinoembryonic antigen are non-specific markers and mere elevation of one or the other should not be taken as sufficient evidence to predict TOO.

Karyotypic or Cytogenetic Analysis

Conventional karyotyping can be used in patients in young patients presenting with midline tumor and multiple pulmonary metastasis. Specific chromosome 12 abnormalities in germ cell tumors (e.g., i[12p], del[12p], and multiple copies of 12p) occasionally allowed for the identification of extragonadal germ cell tumors.[23] In sarcoma patients, cytogenetics may help to make the correct diagnosis such as t(2:13) in alveolar rhabdomyosarcoma, t(X:18) in synovial sarcoma, and so on. Few lymphomas also have tumor-specific immunoglobulin gene rearrangements which can be identified with karyotyping.[24]

Table 4 shows the comprehensive summary of assessment in CUP patients.

Management

If primary tumor site found during the evaluation, site-specific therapy is being offered. However, if primary tumor cannot be detected, the patient will be assigned the diagnosis of CUP. It is important to divide CUP patients into 3 subgroups for the better management.

The first group consists of patients who belongs to the favorable subset. This group consists of only 20% of patients, CUP patients. These patients should receive the specific treatment (describe below). The prognosis of these patients is relatively good with a median survival of 12–36 months with cure in many patients.

The second group consists of patients in whom TOO can be predicted accurately with IHC ± MTP. For these patients, site-specific therapy should be offered.

The third group consists of the patient in whom TOO cannot be predicted. For these, we are left with empirical chemotherapy. Prognosis remains poor with a median survival of 6–9 months.

Table 4: Evaluation of cancer of unknown primary patients

Complete clinical history and physical examination
CBC, comprehensive metabolic panel, LDH, and serum markers
CT thorax, abdomen, and pelvis
Mammography in women and PSA in men
PET/CT in selected cases
Pathology: H and E examination with screening IHC markers
MTP assay if small biopsy or IHC inconclusive

CBC: Complete blood count; LDH – Lactate dehydrogenase; CT – Computed tomography; PSA – Prostate-specific antigen; PET/CT – Positron-emission tomography/computed tomography; IHC – Immunohistochemistry; MTP – Molecular tumor profiling

Management of Patients Belonging to a Favorable Subset

It is important to recognize the patients belonging to a favorable subset as the management is specific. As of today, there are 8 subsets in this group and number is increasing year by year. Detail discussion on each subset is beyond the scope of this article, and hence, each subset is briefly discussed below.

Women with peritoneal carcinomatosis

Diffuse peritoneal metastasis is found one of the specific characteristics of ovarian cancer. However, many times, no primary could be detected during laparotomy. This type of peritoneal involvement can be found in patients with gastrointestinal (GI) cancer, lung cancer, and rarely in carcinoma breast. Rarely, male can also be affected. Histological features resemble carcinoma ovary such as papillary serous configuration or presence of psammoma bodies. CA 125 may be raised and incidence is more common in patients of BRCA1 and 2.[25] Bilateral oophorectomy does not prevent the development of peritoneal carcinomatosis.[26] Although the exact TOO is not known, few people believe that it arises from the peritoneal surface (primary peritoneal carcinomatosis) while others believe to arise from fimbriated end of fallopian tubes.[27,28] IHC shows positivity for CK7 with variable positivity for WT1 and PAX8. Treatment consists of standard ovarian carcinoma regimens (surgical cytoreduction followed by taxane/platinum chemotherapy). The outcome remains similar to patients with ovarian cancer.[29]

Women with isolated axillary lymph node metastasis

Whenever an elderly woman presents with isolated lymph node metastasis, occult breast cancer should be the first differential diagnosis. These are mostly postmenopausal women with median age of 50–55 years. The evaluation consists of history and examination including the specific information regarding the risk factors related to carcinoma breast and family history of carcinoma of breast and/or ovary. Bilateral mammography ± ultrasound of breast can detect the primary tumor in 7%–29% of the patients.[30,31] If primary cannot be detected, bilateral breast magnetic resonance imaging (MRI) should be the next investigation.

MRI detects primary in 75%–86% of patients. The sensitivity of MRI is as high as 88%–100%, but the main disadvantage of MRI is the low specificity as low as 35% in some series.[31] Fine-needle aspiration cytology or core-needle biopsy with IHC is the investigation of choice. IHC shows positivity for CK7 and negativity for CK20 in around 90% of patients. Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2) not only help in making the diagnosis but also provide important information during the planning the neoadjuvant and/or adjuvant therapy. Since only 50%–60% of breast cancer are positive for hormone receptor (ER and PR), and hence does not rule out carcinoma breast, if negative. More specific IHC markers such as gross cystic fluid protein 15 may be required in special circumstances. No distant metastasis detected by CT thorax, abdomen, and pelvis patients should be treated on the line of management of carcinoma breast. Patients with cT0N1M0 can be effectively treated with modified medical mastectomy (MRM) with axillary lymph node dissection, whereas patients with cT0N2M0 should receive neoadjuvant chemotherapy followed by surgery. All patients should receive adjuvant chemotherapy and also radiotherapy if indicated. Based on the hormonal receptor and menopausal status, tamoxifen or aromatase inhibitors should be offered. One year of trastuzumab is the standard of care if positive for HER-2.

Even after the surgery, the primary tumor is identified in only two-third of patients only making the surgery of breast futile in one-third of patients. Hence, breast conservation therapy (BCT) in the form of axillary lymph node dissection and chemotherapy followed by radiotherapy to the breast is considered the reasonable option. Although head-to-head prospective comparison study is not available and also not feasible, retrospective analysis of SEER database of women with T0N+M0 breast tumor showed that 10-year cause-specific survival was 75.7% for patients who underwent BCT versus 73.9% for patients who underwent MRM ($P = 0.55$).[32] In short, the breast should receive some treatment either in the form of surgery or radiation.

Men with elevated serum prostate-specific antigen or prostate-specific antigen staining

Serum PSA is an important organ-specific tumor-specific marker in men adenocarcinoma CUP. IHC passivity for PSA is highly specific and sufficient evidence to consider for androgen deprivation therapy (ADT).[33] The principle of treatment is same as applied during the treatment of carcinoma prostate. An elderly male with osteoblastic bone metastasis even with normal PSA can be considered for ADT. MTP is diagnostic in most cases.

Extragonadal germ cell cancer syndrome

Five important components of this syndrome are as follows:[34,35]

- Occurrence in men <50 years of age
- Predominant tumor location in the midline (mediastinum and retroperitoneum) or multiple pulmonary nodules
- The short duration of symptoms (<3 months) and a history of rapid tumor growth
- Elevated serum levels of HCG, AFP, or both
- Good response to previously administered radiation therapy or chemotherapy.

Definitive diagnosis is made by IHC and/or an MTP assay or by testing for specific chromosome 12 abnormalities. Treatment consists cisplatin-based chemotherapy as used in germ cell tumors.

Single site of neoplasm

Metastasis to the only single site in not uncommon. If primary tumor cannot be detected, unusual primary tumor mimicking metastatic disease should be considered. Aggressive local therapy such as surgery, radiation, and radiofrequency ablation can be considered. If TOO can be determined by IHC or MTP, neoadjuvant or adjuvant therapy can be considered.

SCC with cervical, supraclavicular, or inguinal lymph nodes

SCC involving cervical lymph nodes is the most common. In 15% of patients, primary site cannot be detected even after extensive workup. These patients are usually elderly male with a history of tobacco and/or alcohol intake. These patients can be divided into 2 subgroups. Patients with upper and/or middle cervical lymph nodes involvement where primary tumor mostly confined to the head and neck region. Other group being the patients with lower cervical or supraclavicular lymph nodes where the primary tumor mostly assumed to be in the lung. Some people also recommend a unilateral or bilateral tonsillectomy to detect the primary tumor. In small series of 87 patients, the tonsillar primary was detected in 26% of patients.[36]

Management is controversial and mostly depends on nodal staging. In patients with N1 status, neck dissection followed by radiotherapy with or without chemotherapy is usually used. In patients with N2 disease, concurrent chemoradiation is the standard of care followed by neck dissection for residual disease if detected on PET/CT after 12 weeks of chemoradiation. N3 disease receives neoadjuvant chemotherapy followed by concurrent chemoradiation. The primary tumor arises less commonly during follow-up when primary treatment consists of radiotherapy possibly due to the eradication of occult head and neck primary within the radiation field.

Patients with low cervical and supraclavicular nodes have a poor prognosis as compared to patients with upper and/or middle cervical lymph nodes involvement. In absent of no other site of metastasis, concurrent

chemoradiation can be used as 10%–15% of patients can have long-term survival.

In patients who present with the inguinal lymph node SCC, the possible site of primary is the anogenital areas such as cervix, vagina, anal canal, and penis. Physical examination and biopsy of suspected area are recommended. If no primary can be detected, inguinal lymph node dissection with or without radiation therapy sometimes results in long-term survival.

Neuroendocrine tumors

Neuroendocrine tumor (NET) can be low grade which has indolent clinical course while high NET has an aggressive clinical course with poor outcome. Some high-grade NET cannot be detected by H and E examination and requires IHC or MTP assay.

Low-grade NET most commonly involves the liver, lymph nodes, and bones. They secret bioactive amines and associated with various syndromes carcinoid syndrome, glucagonoma syndrome, VIPomas, and Zollinger–Ellison syndrome. Octreotide scan, as well as an upper and lower GI endoscopy, should be performed. Treatment with octreotide long-acting release results in an increase in time to tumor progression with low toxicity.[37] Local therapy (resection of isolated metastasis, hepatic artery ligation or embolization, cryotherapy, and radiofrequency ablation) can be used in single site of metastasis. As targeted therapy being increasingly used, especially when the primary tumor site is pancreas, MTP can be used upfront.

High-grade NET usually involves multiple sites and rarely secrets bioactive amines. Fiber-optic bronchoscopy should be performed if smoking history is present. These tumors are highly responsive to platinum-based combination chemotherapy (mostly with etoposide).[1,38] Median survival is 14 months.

Colorectal cancer profile

Combination chemotherapy when used with targeted therapy (cetuximab and bevacizumab), the survival of metastatic colon cancer patients has increased to 18–24 months. Colon cancer profile as favorable subset was first proposed by Indian origin medical oncologist Dr. Gauri Rajani Varadhachary in lancet oncology as personal view in the year 2008.[39] These patients usually present with liver or peritoneal metastasis with typical IHC staining (CDX2+ and/or CK20+/CK7−) pattern. Varadhachary *et al*. retrospectively analyzed the data of 74 CUP patients with CDX-2-positive tumors. The author concluded that the median survival of patients (*n* - 34), who has IHC consistent with lower GI profile (CDX-2 positive, CK20 positive, and CK7 negative), was 37 months as compared to 21 months in patients (*n* - 40) with IHC suggestive of probable GI profile (CDX-2 positive irrespective of CK20 and CK7 status).[40]

Management of Patients Not Belonging to a Favorable Subset

Before 1990's, the survival of CUP patients remained poor with a median survival of 4–6 months. Between 1990 and 2000 (in the era of empirical therapy), several newer antineoplastic agents with broad spectrum activity come into the market. These includes taxanes, gemcitabine, vinorelbine, irinotecan, topotecan, and oxaliplatin. The combination of platinum agents with any of the above agents became the standard of care. Median survival increased to 9 months.[41] After 2000, better IHC marker, sophisticated imaging technique, and finally, MTP formed the backbone during the evaluation of CUP patients. As a result, TOO can be predicted in the majority of patients and the era of empiric chemotherapy is nearing its end. In few patients, TOO cannot be predicted and empirical therapy remains the standard of care. Most commonly used regimen is the combination of taxane with platinum agent. Patients who are not candidate for chemotherapy best supportive care remains the last option.

When TOO can be predicted accurately, site-specific therapy should be used. For example, a woman presenting with multiple brain metastasis and brain biopsy showed adenocarcinoma. On IHC positive for CK7, TTF-1 and Napsin A almost confirmed the primary in the lung. The treatment should follow the guidelines used to treat patients of carcinoma lung like finding the actionable mutation (epidermal growth factor receptor, anaplastic lymphoma kinase, and ROS1), and treat accordingly if positive, if actionable mutation is absent patients should be offered pemetrexed in combination with platinum agent for 4–6 cycles followed by pemetrexed maintenance till progression.

An important question that we, the treating physician, have in our mind is whether site-specific treatment directed by the results of MTP assays improve the survival in CUP patients?

A prospective trial at the Sarah Cannon Research Institute, by Hainsworth *et al*., newly diagnosed 289 CUP patients were enrolled and tumor biopsy specimen was tested with a 92-gene RT-PCT-based MTP assay. One hundred and ninety-four patients received assay-directed site-specific treatment. Median survival among these patients was 12.5 months as compared to 9 months in historical controls.[42]

Conclusion

CUP is a real entity, it exists and should not be a source of mental trauma either to pathologist or to the treating physician. A panel of IHC markers can predict the accurate TOO in most of these patients. MTP is a valuable tool when the IHC is inconclusive or available tissue is small. The use of TOO directed site-specific therapy definitely improves the survival. Targeted therapy also being used

more commonly based on TOO. As immunotherapy is coming up in most of the tumor as an effective therapy, this can be a new ray of hope for CUP patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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