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New rising entities in cancer of unknown primary: Is there a real therapeutic benefit?

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ABSTRACT

Cancers of Unknown Primary Site (CUP) account for approximately 1–3 % of all malignant neoplasms. It represents a heterogeneous group of malignancies without a detectable primary and is characterized by aggressive clinical behavior. Patients with CUP are presumably categorized into prognostic subsets according to their clinical and pathological characteristics. The majority of these patients are chemoresistant and treated with empiric chemotherapy regimens which yield limited survival. Recent diagnostic advances have led to the identification of a higher percentage of culprit primaries among which colorectal, lung and renal tumors. The empiric CUP regimens may be suboptimal in these patients which explain in part their poor prognosis. In the absence of prospective randomized studies to prove the benefit of site-specific therapy in these subsets, we reviewed the literature to assess whether CUP with colorectal, lung and renal - profiles should be treated similarly to the correspondent primary tumors.

1. Introduction

Cancers of unknown primary (CUP) are defined by metastatic cancer with no identifiable primary site following adequate evaluation (Fizazi et al., 2015). The standard diagnostic procedure includes a detailed history and physical examination, blood tests, expert pathological review, and imaging using computerized tomography of the chest, abdomen, and pelvis (Fizazi et al., 2015). These recommendations led to better identification of the culprit primary as manifested in the declined incidence of CUP between the historical series (3% - 5%) and the recent reports (1 %–2%) (Rassy and Pavlidis, 2019). CUP remains a deadly disease and constitutes the seventh to eighth cause of mortality in patients with cancer (Pavlidis and Pentheroudakis, 2012).

Patients with CUP are categorized into two prognostic subgroups according to their clinicopathologic characteristics (Pavlidis and Pentheroudakis, 2012). The majority of patients with CUP (80 %–85%) belong to unfavorable subsets, with a modest sensitivity to therapy and median overall survival (OS) of generally 6–10 months (Pavlidis and Pentheroudakis, 2012). In this subset, two prognostic groups are identified according to the performance status (0 or 1) and lactate dehydrogenase (LDH) level (Culine et al., 2002). The one-year survival rate is 53% for good-risk patients and 23% for poor-risk patients. The treatment of this subset consists of empiric broad-spectrum chemotherapy including carboplatin plus paclitaxel or gemcitabine plus cisplatin (Pavlidis, 2007). On the other hand, a minority of patients with CUP (15 %–20 %) harbors a chemosensitive disease and has better long term outcomes (Pavlidis and Pentheroudakis, 2012). The favorable risk cancer subgroup includes patients with neuroendocrine carcinomas of unknown primary, peritoneal adenocarcinomatosis of a serous papillary subtype, isolated axillary nodal metastases in females, squamous cell carcinoma involving nonsupraclavicular cervical lymph nodes, single metastatic deposit from unknown primary and men with blastic bone metastases and PSA expression (Fizazi et al., 2015; Pavlidis and Pentheroudakis, 2012). These patients are treated according to the

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equivalent primary guidelines for metastatic disease.

The current precision medicine era has reclassified more patients with CUP into the favorable prognostic subset, subsided the role of empiric therapy and suggested a potential role for targeted therapies (Rassy et al., 2018; Rassy and Pavlidis, 2018; Greco et al., 2013). New favorable subsets of CUP seem to emerge including colorectal, lung and renal CUP which underlies specific treatments. In this framework, we review the available literature to assess whether CUP with colorectal, lung and renal - profiles should be treated similarly to the correspondent primary tumors.

2. CUP with a colon-cancer profile

CUP with a colon-cancer profile (CUP-CCP) is increasingly being recognized as a distinct favorable subset (Fizazi et al., 2015; Pavlidis and Pentheroudakis, 2012). It consists of (1) adenocarcinoma histologically compatible with a colorectal primary site, (2) primary intra-abdominal metastases and (3) typical immunohistochemistry (IHC) tumor staining (cytokeratin [CK] 20+, CDX2+ and CK7-). CK20 expression is seen in 70–100 % of colorectal cancer and when associated with CK7 negativity has a specificity of 97% in predicting colorectal carcinomas (Bayrak et al., 2012; Blumenfeld et al., 1999). Microsatellite-high (MSI-H) colon tumors and poorly differentiated tumors have low levels of CK20 expression (Kende et al., 2003; McGregor et al., 2004). CDX2, a nuclear transcription factor that is the product of a homeobox gene necessary for intestinal organogenesis, is expressed in almost 97% of colorectal carcinomas (Barbareschi et al., 2003). The concordance of molecular profiling and IHC is around 64.7% (Varadhachary et al., 2008b).

2.1. The applicability of colon-like regimens in CUP

The activity of colon-like regimens combining capecitabine, 5-fluorouracil, irinotecan, and oxaliplatin, have been addressed in multiple phase II trials enrolling patients with poor prognostic subsets of CUP (Golfinopoulos et al., 2007). These regimens yielded an ORR of 35–45% and a median OS of 15–20 months in patients with advanced colorectal cancers (Golfinopoulos et al., 2007). However, treatment-naïve patients without a colon-like profile had been uniformly modest results showing an objective response rate (ORR) of 11.7–35 %, progression-free survival (PFS) of 2.5–3 months and OS of 7.5–9.5 months (Table 1). Similarly, second-line chemotherapy with 5-FU/LV or oxaliplatin plus capecitabine has no impact on survival (Table 1). Taken together, colon-line chemotherapy regimens are disappointing in the frontline and second-line treatment of patients with poor prognostic subsets of CUP.

On the other hand, patients with CUP attributed to a colorectal culprit and treated with empiric CUP regimens have suboptimal outcomes and would probably benefit from a colon-like chemotherapy regimen (Table 2).

2.2. The applicability of colon-like regimens in CUP-CCP

An accurate tissue of origin assignment is of potential clinical importance because standard regimens for advanced colon cancer differ substantially from empiric CUP regimens. The relatively site-specific colorectal chemotherapy regimens have improved the prognosis of patients with colorectal carcinoma.

The outcome of patients with CUP-CCP as defined by IHC has been initially reported by two case series. Varadhachary et al. reported on three patients that were treated with colon-like chemotherapy: two patients with metastatic disease alive at 24–40 months and one patient receiving adjuvant treatment with no recurrence at 20 months follow up (Varadhachary et al., 2008a). One patient received frontline empiric CUP regimens but received colon-like chemotherapy at progression and remains alive at 40 months (Varadhachary et al., 2008a). The largest

Table 1
Prospective trials of patients with CUP treated with colon-like regimens.

Regimen	Regimen schema	Line of treatment	N	ORR	PFS	OS
Oxlri Briasoulis et al. (2008)	Oxaliplatin 80 mg/m^2 followed by irinotecan 160 mg/m^2 administered every 3 weeks	First-line	47	13%	2.7 months	9.5 months
FOLFOX-6 Shin et al. (2016)	Oxaliplatin 100 mg/m^2 and leucovorin 200 mg/m^2 as a 2-h infusion followed by bolus administration of 5-fluorouracil 400 mg/m^2 and continuous infusion of 5-fluorouracil 2400 mg/m^2 every 2 weeks	First-line	23	35%	3 months	9.5 months
CapOx Schuette et al. (2009)	Capecitabine 1000 mg/m^2 twice daily orally for 2 weeks and oxaliplatin 130 mg/m^2 intravenously day 1, repeated every three weeks at a maximum of 6 cycles	First-line	51	11.7%	2.5 months	7.5 months
CapOx[a] Møller et al. (2010)	Capecitabine 1,000 mg/m^2 twice daily orally for 2 weeks and oxaliplatin 130 mg/m^2 intravenously day 1, repeated every three weeks	Second-line	25	13%	2.3 months	3.9 months
CapOx Hainsworth et al. (2010a)	Capecitabine 1000 mg/m^2 twice daily orally for 2 weeks and oxaliplatin 130 mg/m^2 intravenously day 1, repeated every three weeks	Second-line	48	19%	3.7 months	9.7 months
5FU/LV Culine et al. (2001)	Leucovorin 200 mg/m2 as a 2 h infusion followed by bolus 5-FU 400 mg/m2 and a continuous infusion of 5-fluorouracil 1200 mg/m^2 every 2 weeks.	Second-line	25	0%	Not reported	3 months

[a] 76% of the patients had a histopathological assessment favoring a gastrointestinal primary.
N: number of patients; ORR: objective response rate; OS: overall survival; PFS: progression free survival.

Table 2
The outcomes of patients with CUP-CCP according to treatment regimens and line of treatment.

Author	Colon cancer profile assignment	Follow-up	First-line treatment	N1	ORR1	Second-line treatment	N2	ORR2	OS
Varadhachary et al. (2008a)	Immunohistochemistry	Retrospective	Colon-like chemotherapy	3	100%	NR	NR	NR	Alive at 20-36 months
		Retrospective	Empiric CUP regimens	1	NR	Colon-like chemotherapy	1	100%	Alive at 40 months
						1 patient received bevacizumab			
Varadhachary et al. (2008b)	Molecular profiling	Retrospective	Empiric CUP regimens	12	16.7%	NR	NR	NR	0.5-29 months
		Prospective	Empiric CUP regimens	4	25%	Colon-like chemotherapy	3	100%	8-38 months
		Prospective	Colon-like chemotherapy	6	100%	Colon-like chemotherapy	3	100%	9-31 months
								1 patient not evaluated	
Greco et al. (2012)	Molecular profiling	Prospective	Empiric CUP regimens	10	50%	Colon-like chemotherapy	5	80%	3-60 months
						Empiric CUP regimens	2	0%	21-30 months
			Colon-like chemotherapy	21	84.2%	Colon-like chemotherapy	6	60%	5-68 months
					2 patient not evaluated			1 patient not evaluated	
Hainsworth et al. (2012)	Molecular profiling	Retrospective	Colon-like chemotherapy	24	50%	Colon-like chemotherapy	8	50%	
			Empiric CUP regimens	18	17%	Colon-like chemotherapy	8	50%	

CUP-CCP: cancer of unknown primary with colon cancer profile; N1: number of patients in the first-line setting; N2: number of patients in the second-line setting; ORR1: objective response rate of the first-line treatment; ORR2: objective response rate of the second-line treatment; OS: overall survival; PFS: progression-free survival.

series includes 74 patients of whom 53 received a frontline colon-like chemotherapy (Varadhachary et al., 2014). The median OS was 37 months for patients with tumors consistent with a colorectal profile (CK20+/CK7- and CDX2+) and 21 months for those with a probable colorectal profile (CK20+ irrespective of CK7 and CDX2 status). Univariate analysis showed that the choice of the chemotherapy regimen did not correlate to OS (HR = 0.53; 95% CI 0.22–1.22) (Varadhachary et al., 2014).

Four retrospective studies evaluated the outcome of CUP-CCP as defined by molecular profiling (Table 2). The largest series of CUP-CCP include 42 patients among which 32 had received either first- or second-line colon-like regimens (Hainsworth et al., 2012). The ORR was 50% and the median OS was 27 months. Patients receiving frontline empiric CUP regimens had an ORR of 17% (Hainsworth et al., 2012). Median PFS for patients receiving frontline treatment with colon-like regimens and empiric CUP regimens was 8.5 months and 6 months, respectively ($p = 0.11$). The median OS for patients receiving colon-like chemotherapy is 27 months (Hainsworth et al., 2012).

Another series of 32 patients treated with colon-like chemotherapy (21 patients in the first-line and 11 patients in the second-line) or empiric CUP chemotherapy (10 patients in the first-line and 2 patients in the second-line) showed an ORR of 69% (22 of 32) to first-line treatment and 54% (7 of 13) to second-line chemotherapy (Greco et al., 2012). The median OS was 21 months for the entire population and 22 months for patients receiving colon-like chemotherapy regimens as first-line and/or second-line therapy (Greco et al., 2012).

A prospective trial from the Sarah Cannon Research Institute has reported on the site-specific treatment of 289 patients with CUP among which 28 were considered to have a colorectal primary according to a 92-gene reverse transcriptase-polymerase chain reaction cancer classification assay (Hainsworth et al., 2013). Patients treated with FOLFOX or FOLFIRI plus bevacizumab achieved a median OS of 12.5 months (Hainsworth et al., 2013).

In a smaller series, 23 patients were included among which 6 were treated with colon-like chemotherapy. The ORR was 100% and the OS ranged between 9 and 31 months (Varadhachary et al., 2008b). Among the 17 patients treated with empiric CUP regimens, the ORR was 17.6% and the OS range varied between 0.5 and 38 months. The three patients that received second-line treatment achieved partial responses when salvaged with colon-like regimens (Varadhachary et al., 2008b).

3. CUP with a lung-cancer profile

Lung cancer is the most common primary culprit in the autopsy series of patients with CUP (Pentheroudakis et al., 2007). CUP patients with a lung-cancer profile (CUP-LCP) often present with adrenal, liver and cerebral metastases. It consists of non-small cell lung cancer subtype including squamous cell carcinoma and predominantly adenocarcinoma. The typical IHC pattern of adenocarcinoma stains positively for TTF1 and CK7, and negatively for CK20 but can also be encountered in thyroid and neuroendocrine cancers (Fizazi et al., 2015). TTF1 is a master regulatory transcription factor for tissue-specific genes that is expressed physiologically in the normal lung as it plays a decisive role in the maintenance of the functions of terminal respiratory unit cells. Its expression is a highly specific marker for primary lung adenocarcinomas and is reported in 70–80 % of lung adenocarcinomas (Kim et al., 2018). The combination of TTF1 and CK7 has a sensitivity of 96% and a specificity of 73% in predicting lung adenocarcinoma (Gurda et al., 2015). Several molecular profiling has also been evaluated (Hainsworth et al., 2013; Varadhachary et al., 2008b) with one series reporting an agreement rate of 74% between molecular profiling and IHC in lung cancer (Greco et al., 2013). Among patients with CUP in whom a latent lung cancer was identified, the primary was correctly identified by IHC in 40% and molecular profiling in 50% (Greco et al., 2013).

Table 3
Prospective trials of patients with CUP treated with lung-like regimens.

Trial	Regimen	Regimen schema	Line of treatment	N	ORR	PFS	OS
Balana (2003)	Cisplatin- Gemcitabine – Etoposide	cisplatin 70 mg/m^2 D1, etoposide 70 mg/m^2 on D1,D2, gemcitabine 700 mg^2 D1, D8, administered every 3 weeks	First-line	30	36.6%	NR	7.2 months
Culine et al. (2003)	Cisplatin-Gemcitabine	Gemcitabine 1,250 mg/m^2 D1, D8 ; cisplatin 100 mg/m^2 administered every 3 weeks	First-line	40	55%	NR	8 months
Park (2004)	Cisplatin-Paclitaxel	paclitaxel 175 mg/m^2 and cisplatin 60 mg/m^2 administered every 3 weeks	First-line	37	42%	4 months	11 months
El-Rayes et al. (2005)	Carboplatin-paclitaxel	Paclitaxel 200 mg/m^2 and carboplatin AUC 5 administered every 3 weeks	First-line	22	23%	4.1 months	6.5 months
Pittman et al. (2006)	Carboplatin - gemcitabine	Carboplatin AUC5 D8 – Gemcitabine 1000 mg/m^2 D1, D8, administered every 3 weeks	First-line	51	30.5%	4.2 months	8.5 months
Hainsworth et al. (2010b)	Carboplatine-Paclitaxel-Etoposide	Paclitaxel 200 mg/m2 D1; carboplatin AUC6 D1; etoposide 50 mg alternating with 100 mg po, days 1 to 10, administered every 3 weeks	First-Line	93	18%	3.3 months	7.4 months
Gross-Goupil et al. (2012)	Cisplatin-Gemcitabine	Gemcitabine 1,250 mg/m^2 D1, D8 ; cisplatin 100 mg/m^2 administered every 3 weeks	First-line	25	19%	5 months	11 months

AUC: area under the concentration-time curve; D: day; N: number of patients; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.

3.1. The applicability of lung-like regimens in CUP

The CUP-LCP entity is categorized among the poor prognosis CUP subsets and treated with empiric CUP regimens. The commonly recommended options include carboplatin plus paclitaxel or gemcitabine plus cisplatin which are historically considered the standard of care in the treatment of metastatic lung cancer (Fizazi et al., 2015). These regimens achieved an ORR ranging between 18–55%, PFS of 3.3–5 months and OS of 6.5–11 months (Table 3). Similarly, before the era of immunotherapy patients with advanced lung cancer had an ORR of 30–45% and a median OS of 8–11 months (Baggstrom et al., 2007). To the best of our knowledge, the antitumor activity of pemetrexed was not assessed in patients with CUP.

The advances in targeted therapies and immunotherapy have transformed the treatment arsenal of non-small cell lung cancer where driver alterations and PDL-1 expression are key factors in treatment decisions (Planchard et al., 2018; Rassy et al., 2019a). Driver alterations known in lung adenocarcinomas have been reported in CUP such as EGFR alterations in 1–6 %, BRAF mutations in 3–6 % and ALK rearrangements in 0.7–1 % (Rassy and Pavlidis, 2018; Löffler et al., 2016; Ross et al., 2015a; Varghese et al., 2017). Multiple case reports showed a potential activity for targeted therapy in CUP (Table 4). Two phase II trials have also been conducted in this regard (Table 5) but did not report on the percentage of driver alterations namely EGFR mutations (Hainsworth et al., 2007, Hainsworth et al., 2009). The largest includes 60 patients with CUP (adenocarcinoma, poorly differentiated carcinoma, and poorly differentiated squamous carcinoma) treated with a combination of bevacizumab plus erlotinib with paclitaxel plus carboplatin for four cycles followed by bevacizumab plus erlotinib maintenance (Hainsworth et al., 2009). The ORR was 53%, the median PFS was 8 months and OS was 12,6 months (John D. Hainsworth et al., 2009). A smaller series of 51 patients with CUP (adenocarcinoma, poorly differentiated carcinoma, and poorly differentiated squamous carcinoma) treated with bevacizumab plus erlotinib yielded an ORR of 10%, median PFS of 3.9 months and OS of 7.4 months (Hainsworth et al., 2007).

Immune checkpoint inhibitors have improved the OS in the first- and second-line setting of patients with non-small cell lung cancer that lack targetable driver alterations (Rassy et al., 2019a). Unfortunately, the published experience of immune checkpoint inhibitors in patients with CUP is limited to case reports (Gröschel et al., 2016; Kato et al., 2017; Röe and Wahl, 2017) although CUP constitutes a group of highly heterogeneous tumors which renders immunotherapy a very attractive option. The currently ongoing trials are evaluating pembrolizumab monotherapy in poor-prognosis CUP (NCT03391973) as well as pembrolizumab and concurrent radiation in patients with previously treated CUP (NCT03396471). Some studies evaluated the biomarkers of CUP in regards to immune therapy: tumor PD-L1 expression was detected in 22% (SP142 antibody threshold for positivity 5% in cancer cells), TML-high in 11.8%, and MSI-high in 1.8% (Gatalica et al., 2018).

3.2. The applicability of lung-like regimens in CUP-LCP

The CUP-LCP is increasingly being recognized as a distinct entity with several studies trying to report on the outcome of these patients especially that platinum-based doublets are no longer the standard treatment for all non-small cell lung cancer patients (Planchard et al., 2018). The prospective trial from the Sarah Cannon Research Institute enrolled 27 patients with CUP that were considered to have a lung primary their gene expression profile (Hainsworth et al., 2013). These patients were treated with platinum-based doublets plus bevacizumab which achieved a median OS of 15.9 months (Hainsworth et al., 2013). A smaller series of 18 patients with lung profile according to a 10-gene reverse transcriptase-polymerase chain reaction assay has also been reported (Varadhachary et al., 2008b). The carboplatin-based regimens (13 patients received paclitaxel, carboplatin, and etoposide) yielded an

Table 4
Case reports of patients with adenocarcinoma CUP treated with EGFR and ALK inhibitors.

Authors (year)	Age (years) / gender	Pathology	Targetable mutation	Treatment	Best outcome
Tan et al. (2013)	50 / male	Poorly differentiated carcinoma	EGFR L858R exon 21 mutation	Gefitinib / first line	Partial response
Yamada et al. (2012)	53 / female	Adenocarcinoma	EGFR mutation	Gefitinib / third line	Partial response
Zhu et al (2013)	45 / female	Poorly differentiated adenocarcinoma	NR	Gefitinib / third line	Stable disease
Yasui et al. (2014)	75 / male	Adenocarcinoma	NR	Erlotinib + chemotherapy + bevacizumab / first line	Progressive disease
Chung et al. (2014)	50 s / female	Poorly differentiated adenocarcinoma	ALK rearrangement	Crizotinib / first line	Complet response
Palma et al. (2014)	59 / female	Adenocarcinoma	MET amplification	Crizotinib / second line	Partial response
Ross et al. (2015a, 2015b)	50 s / female	Poorly differentiated adenocarcinoma	MET amplification	Crizotinib / second line	Partial response
Hainsworth and Greco (2016)	43 / female	Adenocarcinoma, signet ring	ALK arrangement	Crizotinib / second line Lorlatinib / third line	Partial response
Yamasaki et al. (2018)	67 / male	Poorly differentiated adenocarcinoma	EGFR exon 19 deletion	Erlotinib / first line	Partial response

NR: not reported.

ORR of 38.9% and median OS of 9 months (Varadhachary et al., 2008b).

4. CUP with a renal-cancer profile

CUP with a renal cell carcinoma profile (CUP-RCC) is described in 5% of patients with CUP syndrome in autopsy series (Pentheroudakis et al., 2007). Patients present heterogeneous clinical manifestations with metastatic sites involving the lungs, bones, lymph nodes, liver, adrenal glands, and brain. Uncommon metastatic sites have been reported in the nose and soft tissues (Bhatia et al., 2010; Walton et al., 2019). Ectopic kidney localizations complicates the identification of the primary tumor culprit (Terada, 2012). Tissue examination shows morphological features of renal cell carcinoma, mostly clear-cell, papillary and chromophobe which can be associated with rhabdoid and sarcomatoid components (Greco and Hainsworth, 2018). Poorly differentiated carcinomas or adenocarcinomas can also be encountered but in the absence of clinical suspicion for renal cell carcinoma, CUP-RCC can be missed as specific IHC are not routinely performed (Greco and Hainsworth, 2018).

The IHC patterns vary between the different RCC subsets as CK20 and CK7 stain positively for clear-cell RCC whereas CK7 stains negatively for papillary and chromophobe RCC (Bahrami et al., 2008; Shen et al., 2012). RCC marker, CD10, and PAX8 are useful markers for CUP-RCC diagnosis work-up (Fizazi et al., 2015; Shen et al., 2012). RCC marker is a normal human proximal tubular brush border glycoprotein that stains positively in 85% of clear-cell RCC and more than 95% of papillary RCC (Avery et al., 2000; McGregor et al., 2001). CD10 stains positively in 90% of RCC with a diffuse cytoplasmic or membranous pattern (Chu and Arber, 2000). PAX 8 and vimentin usually stain positively in clear-cell and papillary RCC (Shen et al., 2012).

Molecular alterations can also help to the diagnosis of CUP-RCC. For example, SETD2 BAP1 and PBRM1 are frequently altered in clear-cell and papillary RCCs (Linehan et al., 2016; The Cancer Genome Atlas Research Network, 2013), VHL inactivation is found in more than 80% of clear-cell RCC (Nickerson et al., 2008) and MET amplification is present in more than 80% of type 1 papillary RCC (Albiges et al., 2014). Molecular profiling using a 92-gene molecular cancer classifier assay performed in a series of 539 CUP patients classified 24 tumors as CUP-RCC whereas standard pathologic examination only identified 5 CUP-RCC cases (Greco and Hainsworth, 2018).

4.1. The applicability of renal-like regimens in CUP

The available data reporting on the efficacy of renal-like regimens such as tyrosine kinase inhibitors, mTOR inhibitors, and immune checkpoint inhibitors in CUP are very sparse. An observational study of 286 patients has reported on the outcome of 92 patients with CUP treated with sunitinib which achieved a median OS of 11.9 months (Ma et al., 2016). A phase II trial has evaluated the efficacy of a standard CUP regimen, carboplatin plus paclitaxel, in addition to everolimus in patients with CUP (Yoon et al., 2016). Forty-six patients with a majority having distant metastases to the liver, lung, or bone and tumors exhibiting poor/anaplastic differentiation were included. The ORR was 36% and the median PFS and OS were 4.1 and 10.1 months respectively (Yoon et al., 2016). As discussed previously, the evidence supporting the efficacy of immune checkpoint inhibitor-based regimens in CUP is weak but trials are currently ongoing in this regard.

4.2. The applicability of renal-like regimens in CUP-RCC

The identification of patients with CUP-RCC is essential to optimize their management because the treatment options for advanced RCC do not overlap with the empiric chemotherapy regimens used usually for CUP (Escudier et al., 2019; Fizazi et al., 2015). Patients with CUP-RCC treated with CUP-like regimens usually do not achieve any response

Table 5
Trials of patients with CUP treated with EGFR tyrosine kinase inhibitors-based combinations.

Trial	Regimens schema	Line of treatment	N	ORR	PFS	OS
Hainsworth et al. (2007)	Bevacizumab 10 mg/kg every 2 weeks, plus erlotinib 150 mg orally daily[a]	First-line or more	51	10%	3.9 months	7.4 months
Hainsworth et al. (2009)	Paclitaxel 175 mg/^{2}; carboplatin, AUC 6; bevacizumab 15 mg/kg; administered every 3 weeks plus erlotinib, 150 mg orally daily[a]	First-line	60	53%	8 months	12.6 months

[a]Erlotinib was applied without prior mutation analysis.
AUC : area under the concentration–time curve; N: number of patients; ORR: objective response rate; OS: overall survival; PFS: progression free survival.

(Greco and Hainsworth, 2018; Honda et al., 2014; Overby et al., 2019; Thamcharoen and Chaiwiriyawong, 2013).

Our review of the literature identified 19 case reports of patients with CUP-RCC (Table 1). Four patients had isolated tumor sites that were resected without adjuvant therapy (Bhatia et al., 2010; Heary et al., 2014; Terada, 2012; Walton et al., 2019), only one patient had a local recurrence and was managed with surgery (Heary et al., 2014). One case with oligometastatic disease was not successfully controlled with nephrectomy, bilateral adrenalectomy, and lymph node dissection as the disease progressed and required systemic treatment (Costantino et al., 2016). Patients with metastatic CUP-RCC treated with renal-like regimens achieved outcomes that surpass the survival of those with CUP (Tables 5 and 6).

Two case series have reported retrospectively on the outcomes of patients with CUP-RCC (Table 7). The largest series include 24 patients (18 males and 6 females) with CUP-RCC (6 clear cell RCC, 11 papillary RCC, 7 not assessed) identified by histology or molecular signature (Greco and Hainsworth, 2018). Among the 16 patients treated with frontline renal-like regimens (sunitinib in 9 patients, temsirolimus in 3 patients, bevacizumab in 1 patient, everolimus in 1 patient and interleukin in 1 patient), the ORR was 19%, the median PFS was 8 months and the OS was 14 months. Four patients initially treated with empiric chemotherapy received second-line renal-like regimens but the outcome of these patients was not reported. Overall, 20 of the 24 patients received renal-like regimens and had a median OS of 16 months (range 2-43+ months) (Greco and Hainsworth, 2018).

The smaller series include 10 patients (6 males and 4 females) diagnosed with CUP-RCC according to pathological (clear cell in 30%, papillary type II in 20%, and unclassified in 50%) and clinical examination (Overby et al., 2019). Renal-like regimens (pazopanib in 6 patients, sunitinib in 2 patients and sorafenib in 1 patient) were administered in nine patients. The ORR was 40%, median PFS and OS were 2.5 months and 5.7 months, respectively. The survival analysis according to the International Metastatic Renal Cell Carcinoma Database Consortium showed an OS of 18.6 months in patients with an intermediate-risk score (n = 7) and 2.3 months in a poor-risk score (n = 3) (Overby et al., 2019).

5. Discussion

CUP is a heterogeneous group of metastatic tumors with a distinct natural history that mainly depends on clinicopathological criteria. We have previously reported on new clinical CUP entities that emerge as CUP of adolescents and young adults as well as pathologic entities such as HPV-related squamous cell CUP of the head and neck and HPV-related CUP of the abdomen, pelvis and retroperitoneum (Rassy et al., 2019b; Pavlidis et al., 2019; Rassy et al., 2019c). This review reports on three rising subsets of CUP including colorectal, lung and renal subsets.

The first subset includes patients with CUP-CCP which are classified in the good prognosis subsets of CUP. The survival of patients with CUP-CCP is significantly longer than it is expected for patients with CUP (Tables 1 and 2). Moreover, the ORR seems higher with colon-like chemotherapy than empiric CUP regimens which favors such a personalized approach for patients with CUP-CCP (Tables 1 and 2). Compelling evidence supports the management of these patients with colorectal specific regimens which renders it difficult to assess in randomized trials. However, clinical trials to better define this population are warranted especially that the current guidelines recommend colon-like chemotherapy in patients with CK20+, CK7-, CDX2 + CUP whereas the supporting evidence relies on defining patients with CUP-CCP according to gene expression profiling (Table 2).

The second subset includes patients with CUP-LCP which seems to present a relatively good prognosis. The survival of patients with CUP-LCP parallels the survival of non-small cell lung cancer in the historical series before the advance of the novel agents such as pemetrexed, targeted therapies and immune checkpoint inhibitors (Baggstrom et al., 2007; Hainsworth et al., 2013; Varadhachary et al., 2008b). In the absence of supportive prospective studies, the available data are limited to case reports and small case series that suggest a potential antitumor activity for targeted therapies in CUP (Tables 4 and 5). On the other hand, reports concerning the activity of immune checkpoint inhibitors in CUP are very sparse and further prospective data are awaited especially among CUP-LCP (Rassy and Pavlidis, 2018).

The third subset includes patients with CUP-RCC which are also considered as poor prognostic CUP and treated with empiric CUP regimens. Our review shows that CUP-RCC probably should be considered as a positive prognostic group when treated with renal-like regimens (Table 5 and 6). The treatment of CUP-RCC with renal-like regimens seems to be feasible and effective but the rarity of such cases is a major burden. Larger series or prospective studies are needed to confirm these data. Further evidence is required using the current standard regimens for metastatic renal cell carcinoma such as nivolumab plus ipilimumab, cabozantinib, pembrolizumab plus axitinib and avelumab plus axitinib (Choueiri et al., 2018; Motzer et al., 2019, 2018; Rini et al., 2019).

The main issue remains the correct identification of these subsets in regards to the IHC panel that should be performed to avoid missing these entities and the use of molecular profiling to identify atypical presentations. A phase II prospective study randomizing site-specific therapy to empiric therapy did not show a statistically significant difference between the two arms although prediction of the original site seemed of prognostic value (Hayashi et al., 2019). Similarly, the phase III trial, GEFCAPI 04 (NCT01540058), has randomized patients into site-specific therapy and empiric chemotherapy (Fizazi et al., 2019). The efficacy outcomes PFS (HR = 0.95; 95% CI 0.72–1.25) and OS (HR = 0.92; 95% CI 0.69–1.23) did not differ between the two arms of the study. The subgroup analysis did not identify a statistically significant difference in OS (HR = 0.74; 9 CI 0.36-1.51)0.36–1.51) between patients who are unlike to respond to empiric CUP regimens. It is noteworthy that 15–20% of patients had a pancreaticobiliary cancer profile. Therefore, treatment for the site-specific arm did not differ from the empiric regimen. However, the tailored treatment seemed to be associated with better outcomes in certain subgroups notably renal cell and colorectal carcinoma (Fizazi et al., 2019). The CUPISCO (NCT03498521) trial may bring useful data on this matter especially by categorizing patients according to these subsets where the molecular advances have transformed the corresponding treatment landscape.

6. Conclusion

Patients diagnosed with CUP - colorectal, lung and renal profiles

Table 6
Case reports of patients with CUP-RCC treated with renal-like CUP.

Author	Age (years) / gender	Pathology	Renal cell carcinoma profile assignment	Tumor sites	Management	Follow up
Akkad et al. (2008)	34 / male	Clear cell RCC / sarcomatoid differentiation	IHC	Lung and pleural; suspicious changes in the left kidney	Resection of left kidney followed by adjuvant immunotherapy	Died after several weeks of progressive disease
Bhatia et al. (2010)	63 / male	Clear cell RCC	IHC	Isolated nose mass	Resection of CUP-RCC	Alive at 12 months; no recurrence
Wayne et al. (2010)	61 / female	Clear cell RCC	IHC	Parotid, pancreas	Parotidectomy and pancreatectomy	Not available
Terada (2012)	81 / male	Clear cell RCC	IHC	Isolated retroperitoneal mass	Resection of CUP-RCC	Alive at 6 months; no recurrence
Choi et al. (2012)	69 / male	Clear cell RCC	IHC	One LN involvement	Radiotherapy followed by sunitinib	Alive at 20 months no evidence of progression
Sorscher and Greco (2012)	53 / male	Papillary RCC	IHC and MP	Diffuse LN involvement	Everolimus / first line	Alive at 11 months; no evidence of progression
Johnson et al. (2012)	71 / male	RCC not specified	IHC	Adrenal gland	Resection of the adrenal gland	Alive at 36 months; no evidence of recurrence
Thamcharoen and Chaiwiriyawong (2013)	37 / male	Papillary RCC	IHC	LN, soft tissue and intraabdominal mass	Sunitinib / third line	Alive at 22.5 months; no evidence of disease progression
Heary et al. (2014)	54 / male	RCC not specified	IHC	T2-4 spine	Initial resection followed by a second surgery 6 months later for recurrence	Alive at 12 months; no evidence of progression
Kumar et al. (2014)	70 / male	Clear cell RCC	IHC	Bone and lung	Sunitinib / first line	Alive at 18 months; no evidence of progression
	69 / female	Clear cell RCC	IHC	The synovium of knee and lung	Sunitinib / first line	Died at 8 months of progression
Honda et al. (2014)	47 / male	Clear cell RCC	IHC	Bone	Sunitinib / third line followed by everolimus and axitinib	Not available
Wei et al. (2015)	43 / male	Clear cell RCC	IHC and MP	Bone and lung	Temsirolimus followed by axitinib then everolimus	Died at 9 months
	55 / female	Clear cell RCC	IHC and MP	LN and lung	Sunitinib followed by temsirolimus	Alive at 7 months; no evidence of progression
Costantino et al. (2016)	68 / male	High-grade RCC	IHC and MP	Adrenal glands, liver, diffuse LN involvement	Resection of the adrenals and nephrectomy and retroperitoneal LN dissection followed by sunitinib at metastasis	Alive at 16 months; no evidence of progression
Nagasaka et al. (2017)	41 / male	Papillary RCC	IHC and MP	Diffuse LN involvement, bone	Palliative radiotherapy followed by Pazopanib	Alive at 6 months; no evidence of progression
	79 / male	Papillary RCC	IHC and MP	Diffuse LN involvement, bone	Sunitinib / second line	Not available
Fayaz et al. (2017)	77 / male	RCC not specified	IHC and MP	Diffuse LN	Pazopanib / first line	Alive at 15 months; no evidence of progression
Walton et al. (2019)	52 / male	Clear cell RCC	IHC	Isolated mass in the soft tissue of the forearm	Resection of CUP-RCC	Alive at 27 months; no recurrence

CUP-RCC: cancer of unknown primary with renal-like profile; IHC: immunohistochemistry; LN: lymph node; MP: molecular profile; RCC: renal cell carcinoma.

Table 7
The outcomes of patients CUP-RCC according to treatment regimens and line of treatment.

Author	Renal cancer profile assignment	Follow-up	First-line treatment	N1	ORR1	Second-line treatment	N2	ORR2	OS
Greco and Hainsworth (2018)	Immunohistochemistry and molecular profiling	Retrospective	Site-specific therapy	16	18.8%	Site-specific therapy	3	NA	14 months
		Retrospective	Empiric CUP regimens	8	12.5%	Site-specific therapy	4	NA	NA
Overby et al. (2019)	Immunohistochemistry	Retrospective	Site-specific therapy	9	40%	Site-specific therapy	3	0%	5.7 months
		Retrospective	Empiric CUP regimens	1	0%	Site-specific therapy	1	NA	Alive at 12 months

CUP-RCC: cancer of unknown primary with renal-like profile; N1: number of patients in the first-line setting; N2: number of patients in the second-line setting; ORR1: objective response rate of the first-line treatment; ORR2: objective response rate of the second-line treatment; OS: overall survival; PFS: progression-free survival; NR not reached; NA: not available.

seem to belong to the good prognostic subsets of CUP. Based on the available data, the treatment of these patients similarly to the correspondent primary tumors seems promising. However, the absence of defining/validated diagnostic criteria for CUP with lung and renal profiles limits the interpretation of the treatment outcomes. Moreover, the available evidence is limited to small number of patients reported in case reports and case series. Questions concerning the identification of these subsets, namely the diagnostic role of gene molecular profiling, and the effectiveness of the new treatment options available in the corresponding primaries need to be answered.

Declaration of Competing Interest

Dr Baciarello: Advisory boards and symposia: Amgen, Janssen Oncology, Sanofi, Astellas-Pharma, Roche. Travel accomodations, expenses: Amgen, Astellas-Pharma, Astra Zeneca, Ipsen, Janssen Oncology, Sanofi, Roche. None declared for the remaining authors.

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