



Urachal carcinoma: towards a precision medicine

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Urachal cancer is a rare and extremely aggressive malignancy deriving from an embryological remnant of the urogenital sinus and allantois. It represents <1% of all bladder cancers, with a prevalence of approximately 0.2% and a higher incidence in males than in females (1,2). About 90% of urachal cancers are adenocarcinomas and half of them share histological and molecular features with colorectal cancer (CRC); indeed, they have a common embryological origin from the cloaca (2).

The 5-year survival rate is less than 50%, with a median survival for locally advanced or metastatic disease ranging between 12 and 24 months (3,4). This poor prognosis can be attributed to the following factors: (I) the tumour originates in the anterior portion of the bladder, thus causing delayed symptoms presentation and compromising an early diagnosis; (II) the molecular pathogenesis of the tumor, as well as its sensitivity to specific chemotherapy treatments or molecular targeted therapies, is largely unknown, and no treatment standardization actually exists. This latter aspect is common to all rare cancers, in which collecting sufficient biological material to perform *in vitro* and *in vivo* biological analyses, and enrolling a sufficiently high number of patients in prospective randomized trials, is a challenge for both scientists and clinicians.

Due to the lack of published randomized trials, there are no reference guidelines for the treatment of urachal cancer. In the case of localized disease, surgically removing the tumour is the only strategy that can guarantee cancer cure in a long-term perspective. The standard surgical approach consists in performing partial cystectomy, bilateral pelvic lymphadenectomy and umbilicus plus umbilical ligament resection (1,3). Local recurrence rate within the first two

years after resection is reported to be of 15% to 41%, with the pelvis, bladder, and the surgical incision or abdominal wall being the most frequent sites of relapse. The most common sites of metastatic spread are the liver, lymph nodes, lungs and bones (particularly the spine) (1,3). Risk factors predicting early tumour relapse are: positive surgical margins, lymph node involvement, high tumour grade and advanced TNM stage. Patients at high risk of local or distant relapse could be potentially treated with adjuvant local or systemic treatments, similarly to what is currently done in the case of CRC or genitourinary tumours arising in the pelvis. However, urachal carcinoma tends to be relatively resistant to radiotherapy (2), while the role of neoadjuvant and adjuvant treatments is still unclear.

While localized disease can give rise to metastatic spread after surgical removal, approximately 30% of patients present with metastatic disease at diagnosis. In this setting, no standard-of-care therapeutic options exist. In different published patient case series, single agent or combination chemotherapy has demonstrated antitumor activity and clinical benefit. The most commonly used chemotherapeutic agents are cisplatin and 5-fluorouracil (4,5), while targeted therapies, including gefitinib, sunitinib and cetuximab have recently demonstrated clinical activity in some patients (6,7). Due to the paucity of published studies and the lack of randomized trials, defining the best therapeutic strategy for individual patients with advanced urachal carcinoma is usually left to the discretion of the treating physician. The result of this common practice is a high treatment heterogeneity and arbitrariness, which results in poor treatment optimization and poorly interpretable results emerging from single, small published results.

The article by Collazo-Lorduy *et al.* reports the case of a young male patient with urachal carcinoma metastatic to the lung, who was successfully treated with cetuximab as a third-line therapy. After cystectomy and two subsequent lines of systemic chemotherapy with gemcitabine-FLP (5-fluorouracil, leucovorin and cisplatin), discontinued because of unacceptable toxicity, and doublet carboplatin-paclitaxel chemotherapy, precociously stopped because of progressive disease, targeted genome sequencing performed on the primary tumour revealed the presence of *EGFR* amplification, which was subsequently confirmed by fluorescent *in situ* hybridization (FISH). Moreover, no *KRAS* gene mutations were detected. The patient was therefore treated with cetuximab monotherapy, and reported a radiological partial response (25% decrease of tumor diameters on computed tomography scans) lasting for about 8 months. Whole-genome sequencing was then performed to better characterize the genetic landscape of the primary tumour. However, no alterations linked with tumour sensitivity/resistance to cetuximab other than *EGFR* amplification were found. Then the authors investigated the prevalence of *EGFR* alterations in nine additional patients, but no *EGFR* mutations or amplifications were found. On the other hand, they found alterations in genes that are often involved in CRC cancerogenesis, and converge on activating the MAPK pathway, such as *KRAS*, *NRAS* and *MAP2KI* activating mutations (8).

Similar data have emerged from a recent molecular analysis published by Módos *et al.*, who also found *BRAF* mutations occurring with a similar frequency as in CRC (9).

It is currently unknown if urachal carcinomas with different molecular profiles result in different biological and clinical behavior. However, based on the accumulating experience in other cancer types, specific gene mutations could have a prognostic (such as the case of *BRAF* mutations in CRC) or predictive (such as *EGFR* mutations in lung adenocarcinomas treated with EGFR inhibitors or *RAS*-mutated CRCs) value (10-12). Understanding the molecular mechanisms driving urachal cancer growth, as well as the genetic alterations conferring sensitivity or resistance to specific therapies, might guide treatment personalization.

Since published data suggest that the molecular landscape of urachal carcinoma could be similar to that of CRC, molecularly targeted treatment could parallel the recent successes obtained in CRC therapy. For this reason, and due to the limited therapeutic options available for urachal carcinoma, routine genomic assessment for actionable mutations may provide useful information to guide

treatment personalization. For example, the absence of *KRAS*, *NRAS* and *BRAF* mutations could predict sensitivity to the EGFR inhibitors cetuximab and panitumumab, while *BRAF* mutations could predict tumor sensitivity to combinations of BRAF inhibitors (e.g., vemurafenib or dabrafenib) with EGFR or MEK 1/2 (e.g., trametinib) inhibitors (13-16).

Despite these promises, the following critical aspects need to be discussed.

Firstly, because of the low incidence of urachal carcinoma, all patients with this form of cancer should be sent to reference centers with the aim of collecting tumour tissue samples to comprehensively investigate the mutational landscape and molecular pathogenesis of this cancer type. Indeed, one crucial aim is to provide the most exhaustive view as possible of occurring genetic alterations and their frequency, so to understand which alterations are worth being routinely assessed and therapeutically targeted.

Secondly, the correct timing for tumour genetic assessment and targeted therapy administration needs to be established. In commonly occurring cancers, such as CRC or lung cancer, randomized trials have been performed to clarify the clinical efficacy of molecular targeted therapies before, after or concomitant with first-, second- or third-line chemotherapy treatments. Results emerged from the studies are not universal, and depend on both tumor site and tumor biology. For example, combination of standard cytotoxic chemotherapy with anti-EGFR monoclonal antibodies has emerged as the most effective first-line treatment in advanced CRC with wild-type *KRAS/NRAS/BRAF*. On the other hand, combining EGFR-mutated small tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib with first line chemotherapy in lung adenocarcinoma has not proven to be more effective than single TKI or chemotherapy treatment (17-21). Due its rarity and the lack of established chemotherapy treatments, it will be impossible to replicate such big studies in urachal carcinoma. For this reason, there will be poor space for rationally combining biological therapies with cytotoxic chemotherapy, and molecular-targeted treatment options will probably consist in single- or combination biological treatments targeting molecular alterations that likely drive cancer growth. One different scenario could emerge in the case that the mutational landscape of urachal carcinoma will be found to significantly overlap with that of CRC. In this case, there is a hope to translate results deriving from big studies in advanced CRC directly to the treatment of urachal carcinoma, including possible combinations of chemotherapeutic treatments

with molecular targeted therapies. However, the fact that sunitinib and gefitinib have shown activity in urachal but not CRC suggests that the genetic landscape, molecular pathogenesis and sensitivity to treatments by these tumors is not completely overlapping (6,7,22,23).

Lastly, the increasing necessity to extend genetic profiling to individualize patient care collides with the high costs of diagnostic tests and currently available molecular targeted therapies. However, this problem is common to all cancer types in this historical period. Once the biology of urachal carcinoma, as well as its disease-relevant and “druggable” targets, will be identified, treatment personalization will allow to restrict genetic/molecular profiling studies and costly treatments to patients more likely to specific patients, while sparing useless analyses and treatments to the remaining patients.

Despite the lack of prospective studies and treatment standardization in patients with advanced urachal carcinoma, the availability of compounds targeting crucial biological pathways, such as EGFR and VEGFR inhibitors, has recently expanded the potential therapeutic armamentarium against this type of cancer. This fact, combined with the availability of sensitive and potent molecular biology techniques that are able to reveal drivers of cancer growth, will likely improve patient outcomes compared to historical data. In the perspective of treatment personalization, it is mandatory to define a clear picture of occurring molecular alterations, so to make specific genetic and molecular tests widely available to patients, and to approve the use of compounds targeting the most frequently deregulated pathways.

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