CORRESPONDENCE

The Diagnosis and Treatment of Cholangiocarcinoma

by Prof. Dr. med. Arndt Vogel, PD Dr. med. Henning Wege, Prof. Dr. med. Karel Caca, Prof. Dr. med. Björn Nashan, Prof. Dr. med. Ulf Neumann in issue 44/2014

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The author declares that no conflict of interest exists.

Isocitrate Dehydrogenase Genes

The molecular classification and taxonomy of malignant diseases, such as the one successfully applied and published by The Cancer Genome Atlas Project TCGA (http://cancergenome.nih.gov/) for urinary bladder and colorectal cancer, adenocarcinoma of the stomach, and glioblastoma multiforme, provides the opportunity to define so-called driver mutations for the various entities and hence to predict the efficacy of drugs and the clinical prognosis. With the recent completion of the specimen collection for cholangiocarcinoma, publication of the results is to be expected in the near future. In an insightful review (1), the authors listed 13 genes which are involved in certain cellular signaling pathways and can be influenced by targeted treatment. Using the latest generation of genome sequencing techniques, promising potential applications were identified for the FGFR and ROS1 signaling pathways and mutations of the isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) genes (2). The latter is very important for two reasons: Of all malignant entities of the gastrointestinal tract, the IDH mutations are only identified in cholangiocarcinoma. The oncometabolite 2-hydroxyglutarate is the product of this mutated enzyme and has been identified as potential surrogate biomarker in patients with cholangiocarcinoma (3). In addition, this marker offers the advantage over the commonly used serum levels of CA 19 – 9 that its concentration is not dependent on the Lewis and secretor genotypes of the blood groups. Cisplatin sensitivity of the cholangiocarcinoma is associated, as in the urinary bladder and non-small-cell lung cancer, with the somatic ERCC2 gene mutations.

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Radioembolization as a Treatment Option

There is one important aspect that needs to be added to this concise and noteworthy review (1) of the diagnosis and treatment of cholangiocarcinoma: Radioembolization is a clinically relevant treatment option in palliative patients after failure of systemic first-line therapy (gemcitabine + cisplatin), even though it is not yet supported by strong evidence.

This method, also known as SIRT (selective internal radiation therapy), represents a locoregional transarterial therapy with Y-90 microspheres causing semiselective internal radiation of the hepatic tumor lesions after intra-arterial application and preferential deposition within the tumor. Prerequisites include arterial (hyper-) perfusion and good angiographic accessibility of the cholangiocarcinoma lesions. Neither tumor size, number of lesions or proximity to vessels, nor portal vein infiltration or thrombosis are limitations or contraindications to its use.

Radioembolization can achieve dramatic remissions with high rates of local tumor control through tumor-absorbed doses of in the order of1000+ Gy (2). For its indication, there are specific requirements with regard to the liver reserve, the general condition (ECOG ≤ 2) as well as liver-dominant total tumor burden, apart from the above mentioned technical prerequisites.

Several studies have documented disease-control rates of 74 to 98% and median survival rates (OS) of 9 to 22 months (3, 4).

It is important to raise awareness of this method because the reader of this review may not consider this option for an eligible palliative patient after failure of the standard chemotherapy regimen. However, this treatment modality may provide tumor control over a period of more than one year with good quality of life to suitable patients. An individual assessment of this option should therefore be mentioned as an alternative to therapeutic nihilism.

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In Reply:

The focus of our review has been on the present clinical practice based on scientific evidence; therefore, promising but currently still experimental treatment approaches have not been discussed in detail (1). In addition, all studies on the molecular and targeted treatment of CCA (particularly EGFR-directed antibodies) have unfortunately not yet been successful. More recently, the BINGO study, a joint study of the Working Group of Internal Oncology (*Arbeitsgemeinschaft Internistische Onkologie*, AIO), evaluating gemcitabine and oxaliplatin with and without cetuximab, did not reveal any relevant improvement in progression-free survival (6.1 months with cetuximab and 5.5 months without cetuximab) (2). Data from the PiCCA study, an AIO-associated study, which only included KRAS wild-type patients for treatment with gemcitabine and cisplatin with and without panitumumab, are not yet available. As with other tumor entities, there is a reasonable expectation, as described by Dr. Tsamaloukas, that treatment-relevant target structures for CCA may be identified by using the latest sequencing techniques. Whether these eventually will be mutations of the isocitrate dehydrogenase 1 and 2 genes will have to be confirmed in clinical studies.

Radiation therapy based on the intra-arterial injection of the beta emitter Yttrium-90—which is encapsulated in microspheres in the case of selective internal radiation therapy (SIRT)—enables local tumor control in arterially hypervascular liver tumors. Therefore, this procedure represents a treatment option for some patients with intrahepatic cholangiocarcinoma (iCCA) too. Due to the lack of randomized and controlled trials, its integration with the treatment algorithm for iCCA is not possible, especially not as an alternative treatment option or as a further treatment after systemic chemotherapy. The available monocentric and non-controlled cohort studies with 24 to 46 patients of Mouli et al. (3), Ibrahim et al. and Saxena et al. (4) showed in summary that SIRT can be performed safely, provided proper patient selection (stabile general condition with ECOG $\leq$ 2, bilirubin serum levels < 2 mg/dL). Especially—and this is also indicated by the data published to date—local tumor control can be achieved in patients with a single, peripheral intrahepatic focal lesion. In this respect we agree with Ezziddin et al. that SIRT for iCCA may be a clinically relevant treatment option for some patients which should be evaluated by an interdisciplinary tumor board As already mentioned in our review, prospective randomized clinical trials will have to be conducted to evaluate the actual value of this treatment, especially in combination with systemic treatments.

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