Targeted agents: how can we improve the outcome in biliary tract cancer?

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The management of biliary tract cancer (BTC) has deeply changed in the past decade. Just few years ago patients with advanced disease had no effective treatment options but supportive therapy. Palliative chemotherapy was often administered in the absence of evidence of efficacy, as no randomized studies were available.

At present the results of two randomized trials have established a new standard of therapy: the combination of gemcitabine and platinum compounds has proven to significantly prolong survival in unresectable patients (1,2). Moreover, the development of new therapeutic modalities, including pioneering targeted therapies, is opening new avenues in the management of BTC (3). Undoubtedly, this represents a timely subject, considering the steps that have been made in different cancer types by adding newer agents. Some phase II studies with targeted agents, mainly anti-EGFR and VEGF drugs, are now available with equivocal results.

If we look at the current knowledge on the molecular basis of BTC, the EGFR pathway seems to fit the prerogatives to be a good setting for targeted agents. The incidence of biological features that might predict response or resistance to anti-EGFR has been studied in preclinical models.

EGFR gene amplifications are detected in approximately 6% of BTC, and EGFR mutations only in 15% (4) suggesting that the majority of patients may lack a biologic requisite of sensitivity to small molecules inhibitors.

On the contrary, KRAS mutations, that are now a validated predictive factor of response to anti-EGFR antibodies in colorectal cancer, occur in 6% to 52% of BTC, being more common in eastern than western countries.

In phase II studies anti-EGFR antibodies cetuximab or panitumumab, associated to chemotherapy produced impressive results in terms of response rate in KRAS wild type patients (5,6). Because of the design of these non-randomized studies, it is impossible to define the real impact of the addiction of monoclonal antibodies to chemotherapy.

More definitive results were expected from randomized studies: however the lack of molecular selection of patients might have blunted the results.

Lee et al. designed a phase III trial in which 268 patients with unresectable cholangiocarcinoma (CC), gallbladder carcinoma (GBC) and ampullary carcinoma (AC) were randomized to receive either gemcitabine-oxaliplatin (GEMOX) alone or in combination with erlotinib as first line treatment (7). The primary endpoint was progression-free survival (PFS). Although a trend in favor of the regimen GEMOX-erlotinib was observed, the study did not meet the primary endpoint; the median PFS was 4.2 months in patients who received chemotherapy only versus 5.8 months in those who had chemotherapy plus erlotinib (P=0.087). The overall survival (OS) was 9.5 months in both treatment arms. It is noteworthy that the addition of erlotinib statistically improved the objective responses (ORs) (P=0.005). This was especially evident in patients with CC. This subgroup had a benefit in PFS as well, even though this difference was marginally significant (P=0.049). On these bases, the authors suggested that patients with CC might benefit more from the addition of erlotinib to chemotherapy.

At the latest ASCO meeting Malka et al. presented similar data from their randomized phase II trial of GEMOX with or without cetuximab (8). The primary endpoint of a better 4-months PFS for the cetuximab-containing regimen was...
met (63% vs. 53%), but data on median PFS and median OS showed no difference between treatment arms.

Both trials had a simple design of 2 arms phase III or phase II, multicenter, open-label studies. The number of patients was adequate to distinguish differences between treatment arms, but in Lee’s trial there was an imbalanced distribution of type of primary tumor, due to the choice of stratification factors. Moreover, the data on subgroups were then obtained retrospectively; in our opinion this issue is quite relevant, as many studies suggest a different biology and chemosensitivity between GBC and CC, so stratification on location is highly recommended.

Some consideration must be made about the rationale of both studies. Lee and colleagues motivated their choice of the combination treatment on the basis of a single agent phase II trial of erlotinib (9) and on the results of erlotinib therapy in pancreatic cancer (10). No phase II randomized trials of GEMOX ± erlotinib has ever been made. Tissue analysis was possible only in few cases, making any conclusion on data for KRAS and EGFR subgroups simply hazardous.

Background for cetuximab therapy seems to be more solid; a couple of reports and phase II trials (5,6) have shown interesting results. Subgroup analysis for KRAS status and site of primary is under way; when available, Malka work might be exploratory for a larger phase III trial.

Thus, at present, studies without patient selection should be regarded as preliminary.

Even though OS in metastatic disease has not significantly improved with the introduction of anti-EGFR therapy, the possibility to obtain higher response rates, if compared to chemotherapy alone, rises the chance to consider the role of these treatments as part of a neoadjuvant program. In the phase II study of Gruenberger with cetuximab in combination with GEMOX, a conversion from unresectable to resectable disease was obtained in 30% of cases (5).

A recent case report has shown how treatment can be driven by knowledge of molecular status; on the basis of HER2 expression investigators proposed a 4th line therapy with trastuzumab and paclitaxel in a patient affected by CC, obtaining an impressing response (11). Small phase II trials in BTC with anti HER2 agents, in the absence of selection on gene expression, had previously shown no activity (12).

The identification of newer pathways in carcinogenesis and progression, such as SRC or ROS (13,14), could pave the way for the introduction of other targeted drugs. If the molecular status is not helpful we should not forget that fit patients might benefit from multi-drugs chemotherapy, as it was proven for pancreatic cancer (15).

The issue of how to improve treatment by adding targeted agents is highly relevant; we firmly believe that the history of BTC can be changed if we detect the specific pathway that is activated in every single patient.

Therefore, what we have learnt from more common malignancies should not be forgotten when designing new clinical trials on BTC; small, well-designed phase II trials might be more relevant than large inconclusive phase III studies.

Patients should be then selected on the basis of gene expression; this is the only way we can make our treatment really “targeted”.

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References


