Re: Design and Endpoints of Clinical Trials in Hepatocellular Carcinoma

The commentary on design and endpoints of clinical trials in hepatocellular carcinoma (HCC) by Llovet et al. (1) gives a relevant contribution to the methodological improvement of clinical research in this setting. We appreciate the panel’s recognition that the proposed treatment algorithm for HCC patients remains based on very low strength of evidence, with a still unmet need for well-designed and well-conducted clinical trials. However, two relevant methodological issues of the paper deserve some comment: the definition of study population and the design of randomized phase 2 trials.

As for the study population, the expert panel stated that all new drugs should first be tested in patients with well-preserved liver function (Child-Pugh A) and only subsequently extended to subjects with more impaired liver function. Including patients with worse liver function would, of course, increase the risk of toxicity and potentially compromise the interpretation of results due to the greater relative impact on prognosis of poor liver function. However, Child-Pugh A patients represent a limited proportion of patients with advanced-stage HCC who are candidates for systemic therapy. Excluding patients with Child-Pugh B from frontline drug development will greatly reduce the generalizability of results. Llovet et al. state that after studies in Child-Pugh A patients, subsequent studies could be conducted in Child-Pugh B patients to assess the safety and confirm the efficacy of new compounds in this population. However, once a drug becomes available in clinical practice, physicians with Child-Pugh B patients will face the difficult decision of whether to deny them the new therapy or expose them to the risk of unacceptable toxicity against an unconfirmed potential benefit. Development of sorafenib in HCC is a good example: the phase 3 trial was limited to Child-Pugh A patients (2), and the information about the effects of sorafenib on patients with Child-Pugh B disease comes from the limited cohort enrolled in the phase 2 study (3). Thus, despite the urgent need for effective systemic treatments in clinical practice, robust demonstration of efficacy of sorafenib in Child-Pugh B patients is still lacking; indeed, some evidence suggests caution in the use of the drug in patients with impaired liver function (4). Clinical trials could be stratified by Child-Pugh class, rather than postponing studies in patients with poorer liver function. Several measures could allow this “frontline” strategy: 1) proper pharmacokinetic evaluation in early trials; 2) separate cohorts in phase 1 trials to identify differential dose-limiting toxic effects; 3) careful safety assessment and early stopping rules; and 4) proper hypotheses in phase 3 trials that take into account the different prognosis of Child-Pugh categories.

As for phase 2 trials with new agents, the expert panel recommended randomized phase 2 trials as proposed in 1994 by Simon et al. (5). However, that publication actually described the selection design, which does not allow a formal comparison among treatment arms and should be used without a control arm (6). More recently, randomized phase 2 trials with a control arm and “relaxed” statistical criteria have been proposed (7), although they would imply a quite large sample size if the 10% statistical significance level suggested by Llovet et al. were to be adopted.

References