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Effective randomized clinical trial design: sequential analysis

Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Sola R, Rodes J, Bruix J, Barcelona Liver Cancer Group. Liver Unit, Digestive Disease Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain.

There is no standard treatment for unresectable hepatocellular carcinoma. Arterial embolisation is widely used, but evidence of survival benefits is lacking. We did a randomised controlled trial in patients with unresectable hepatocellular carcinoma not suitable for curative treatment, of Child–Pugh class A or B and Okuda stage I or II, to assess the survival benefits of regularly repeated arterial embolisation (gelatin sponge) or chemoembolisation (gelatin sponge plus doxorubicin) compared with conservative treatment. 903 patients were assessed, and 112 (12%) patients were finally included in the study. The primary endpoint was survival. Analyses were by intention to treat. The trial was stopped when the ninth sequential inspection showed that chemoembolisation had survival benefits compared with conservative treatment (hazard ratio of death 0.47 [95% CI 0.25–0.91], p = 0.025). 25 of 37 patients assigned embolisation, 21 of 40 assigned chemoembolisation, and 25 of 35 assigned conservative treatment died. Survival probabilities at 1 year and 2 years were 75% and 50% for embolisation, 82% and 63% for chemoembolisation, and 63% and 27% for control (chemoembolisation vs control, p = 0.009). Chemoembolisation induced objective responses sustained for at least 6 months in 35% (14) of cases, and was associated with a significantly lower rate of portal-vein invasion than conservative treatment. Treatment allocation was the only variable independently related to survival (odds ratio 0.45 [95% CI 0.25–0.81], p = 0.02). Chemoembolisation improved survival of stringently selected patients with unresectable hepatocellular carcinoma.
[Lancet 2002;359:1734–1739]

Sufficiently large well-conducted randomized clinical trials (RCTs) are necessary for proper evaluation of therapies. However, in the field of hepatocellular carcinoma (HCC) most studies are uncontrolled or poorly controlled – using historic controls or other types of non-randomized control groups, which may imply a bias – most often in favour of the 'new' therapy. Decision analysis based on Markov modelling is usually based on uncontrolled data and does not represent an alternative to RCTs. Advanced statistical analysis cannot compensate for a lack of relevant data. Thus, at present the evidence of a beneficial effect of some of the therapeutic modalities used in this disease is questionable.

Recently, Llovet et al. [1] published a well-performed RCT comparing arterial embolization and chemoembolization with symptomatic treatment for unresectable HCC. They demonstrated that compared with conservative treatment chemoembolization significantly increased survival. They successfully used the sequential analysis design, which was first described extensively by Wald more than 50 years ago [2]. Since then it has been further developed by other prominent statisticians, in particular Armitage [3] and Whitehead [4]. As the name implies, the method is based on sequential analysis of the data as they accumulate during the trial period. The trial is terminated when the current cumulative outcome achieves a certain magnitude. Thus, the sequential design has the clear advantage of providing an effective stopping rule: as soon as a well-defined result is obtained, the trial is stopped, the two possible results being either a significant difference between the treatments, or no significant difference with a type 2 error risk of overlooking

a given effect less than specified at the planning stage. The design implies a close monitoring of the trial, and the well-defined stopping rule effectively eliminates any unnecessary or undesirable continuation of the trial beyond the point at which one treatment is clearly better than the rival treatment. These features give the sequential design ethical and economical advantages over other trial designs.

Since repeated inspection and testing of the cumulative result implies an increased risk of type 1 error (false positive result), adjustment of the nominal significance level at each test is necessary. The more inspections, the greater the necessary adjustment. Furthermore, the sequential analysis plan depends on the difference (Δ) in effect between the therapies to be determined, the overall type 1 error risk (2α) and the power ($1 - \beta$). The sequential analysis design can be used with any type of endpoint including proportions, quantitative variables and survival data.

In their paper Llovet et al. studied survival – being the primary endpoint – devising their sequential plan and analysis according to the methods of Whitehead using his computer program PEST (Planning and Evaluation of Sequential Tests) [5] version 3.0. This advanced program can adapt the sequential design to fulfil specific needs: (a) stopping for evidence of treatment difference or for lack of difference; (b) stopping only for evidence of treatment difference; (c) stopping in case of evident harm; or (d) stopping as soon as it is evident that insufficient benefit will be seen. It also allows for the sequential design in all final analyses of the trial and provides confidence limits of the result.

Llovet et al. inspected the data at every five deaths, and after the ninth sequential inspection a significant difference in favour of chemoembolization was found when the upper boundary of the sequential analysis diagram was crossed. Adjustment for possible imbalance in prognostic variables between the groups using Cox regression analysis did not change the result.

The work of Llovet et al. illustrates very well the efficiency of the sequential analysis design, which undeservedly is rarely used. A crude MEDLINE search in the field of hepatology disclosed only two other RCTs using this method [6,7]. Hopefully in the future the virtues of this elegant methodology will be more widely recognized. Sophisticated tools for its optimal use have already been developed.

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