News

Overviews and Mega-trials: Two New Initiatives in Colorectal Cancer

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THE FIRST main meeting of the Colorectal Cancer Collaborative Group (CCCG) was held in Oxford on 27 and 28 September 1993. This collaboration of colorectal cancer trialists was initiated in 1992 with the aim of conducting a systematic overview (or meta-analysis) of the data from randomised controlled trials in the disease. Individual patient data were sought from all trials which had assessed any aspect of the primary adjuvant treatment of colorectal cancer, and which began before January 1987. The principal questions addressed in these trials were the effect on survival of 5-fluorouracil (5-FU)-based chemotherapy, of pre- and postoperative radiotherapy, and of various forms of immunotherapy. Preliminary analyses were presented in confidence to a meeting of the collaborating trialists held in Oxford last September. Various extra analyses that were suggested at the meeting are now being undertaken, and it is anticipated that, after an additional period of data collection and correction, the results should be published later this year.

A total of nearly 100 research groups involved in randomised trials of colorectal cancer treatment have been identified by the CCCG Secretariat, and between them they have undertaken approximately 100 relevant trials. By the time of the meeting, individual patient data had been supplied from 58 of these studies, on a total of 20 000 patients. Published data were used, where available, for those trials from which individual patient data had not yet been provided, but even so the total number of patients available for analyses in the overview was just 15 000 randomised between various forms of chemotherapy and no chemotherapy and just 8000 randomised to radiotherapy versus no radiotherapy. Considering that over the period of these trials more than 700 000 patients were diagnosed with colorectal cancer in the U.K. alone, and many millions more worldwide, this is a rather disappointing total. Moreover, since it is known that the early, probably suboptimal chemotherapy regimens tested in these studies have at best only a moderate effect on survival, the numbers studied are barely adequate to answer reliably the question of whether the therapies definitely do improve survival, and are hopelessly inadequate for any reliable assessment of how big the survival benefit of a particular form of chemotherapy might be, or to identify which types of patient might benefit most. Nor is it possible to be sure which of the many pre-1987 chemotherapy regimens tested are the most effective.

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Over the three decades prior to 1987, some 35 000 patients were entered into randomised trials worldwide. When the planned update of the overview is undertaken in 5 years' time, this will be supplemented by a few thousand more patients from trials that began in 1987 or later. However, it is worth noting that in Europe alone, more than 600 000 patients will be diagnosed with colorectal cancer over the next 5 years, and that 400 000 of them will die from their disease. If just a few per cent of these patients could be entered into randomised trials, then the available evidence in the next cycle would become enormously more reliable. Perhaps the main message of the overview, therefore, is that if we are to assess the benefits of current treatment modalities in colorectal cancer truly reliably (e.g. perioperative portal vein infusional therapy, 5-FU biomodulated by folinic acid, etc.), then we will need to enter many many more patients into randomised controlled trials than we have done in the past.

One way of recruiting appropriately large numbers of patients into studies which has proved successful in cardiovascular disease (e.g. the ISIS trials) is to use highly streamlined trial designs (so-called "mega-trials"). The idea of these studies is to make it just about as easy to enter patients into the study as it would be to treat them outside of the study. Two such mega-trials are currently under way in the U.K. The AXIS trial which is assessing the value of a 1-week intraportal infusion of 5-FU, and also the effect of radiotherapy, has already accrued more than 2000 patients. AXIS aims to reach its recruitment target of 4000 within the next 2 years. A second mega-trial, QUASAR, investigating systemic chemotherapy, is due to be launched in London on 21 February. The two questions being addressed in QUASAR are, "Which patients should be treated?" (randomising systemic chemotherapy versus untreated control among patients for whom there is substantial uncertainty about whether or not to use chemotherapy) and, "Which chemotherapy is best?" (randomising 5-FU with either high dose or low dose folinic acid and with either levamisole or placebo). To yield clear reliable answers, QUASAR will need to recruit some 8000 patients over about 3 years. Such numbers can only be achieved with really widespread international collaboration, and both trials would welcome new participants. Further information on AXIS can be obtained from Alison McQueen, MRC Cancer Trials Office, 5 Shaftesbury Road, Cambridge CB2 2BW, U.K. (fax: +44-(0)223-311844), and on QUASAR from Mandy Collingwood, CTSU, Radcliffe Infirmary, Oxford OX2 6HE, U.K. (fax: +44-(0)865-58817). Further information on the Colorectal Cancer Collaborative Group can be obtained from Mike Clarke also at the CTSU.