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EDITORIAL

Chemotherapy for Ovarian Cancer: Is There a Best Buy?

Although most oncologists accept that the best method of postoperative treatment for advanced ovarian cancer is chemotherapy rather than radiotherapy, the most effective single agent or combination of agents to be used remains a matter for discussion. In the United States medical opinion favors combination chemotherapy including cisplatin plus cyclophosphamide with or without additional Adriamycin, but in some parts of Europe centers have taken the view that cisplatin alone, given in reasonably high dosage (75–100 mg/m^2 at least monthly) is just as effective. The latter view appeared to be supported by the much quoted work of Levin and Hryniuk [1], suggesting that for early ovarian cancer, only cisplatin doses were important to response rate and survival. However, a firm belief that combinations of drugs are always superior to single agents remains. Unfortunately, in the case of ovarian cancer this matter has still not been resolved.

In 1987 the Italian Group published a multicenter trial [2] that tried to answer this question by comparing CAP (cyclophosphamide, Adriamycin, cisplatin) with CP (cyclophosphamide, cisplatin) and cisplatin alone (P). Their conclusion was that while response rate was certainly higher with CAP, complete responses were similar and survival was not significantly improved after a median follow-up time of 21 months. This group has now updated the trial and the results are reported in this issue. Interpretation of their new data, however, needs to be looked at in conjunction with the 1987 publication because some details of the study have not been presented again. The most important points are that each arm had more than 160 patients entered and analyzed, and after 6 months of treatment further therapy was often offered. If complete response was achieved patients were randomized to receive either ^{32}P or no treatment, and those with microscopic disease at the end of 6 months or who had previously been shown to have involved lymph nodes were given "moving strip radiotherapy." Lastly patients in partial remission "continued on or were crossed over to CAP" for a further 6 months. Thus many patients had more than 6 months of therapy either with ionizing radiation or chemotherapy. Indeed many (perhaps 51 of 173 patients) commenced on cisplatin alone were then given further CAP. Thus many patients who were doing reasonably well in fact had more than 6 months of therapy and possibly up to 12 months. Some also had radiotherapy. The crossover from cisplatin to CAP makes the problem of interpretation of the study more difficult although the reasons for the crossover are understandable.

Statisticians may say that although more patients were entered into this study than in many reported ovarian cancer trials there were still not enough to show a 10 or 20% survival difference. Nevertheless the update shows that large differences between each arm are not seen despite a much longer follow-up (median, 80 months). The problems of trials with relatively small numbers of patients are well known and attempts are now being made to overcome these difficulties by using the method of meta-analysis. This type of trials analysis also has pitfalls, however, not least of which is the lack of description of each trial in detail. Many trials reported by the MRC [3] recently were inherently flawed by crossover between trial arms similar to that reported by the Italian group. Indeed even using meta-analysis the MRC Unit was unable to find sufficient randomized studies comparing cisplatin combination with cisplatin as a single agent to be sure that the difference of 15% reduction in the risk of death that they found was real since most of the patients came from the Italian Group study now updated here.

Since, despite all the caveats, there are no large survival differences between combination chemotherapy using CAP or CP and P, quality of life measurements take on greater importance and unfortunately we do not have any analysis of this. The authors do suggest, however, that in choosing a regimen for the treatment of patients with advanced ovarian cancer, toxicity and cost should be taken into account. One wonders whether this will be done in the large number of patients being treated outside the clinical trials. Unfortunately it is more likely that preconceived opinions will triumph over the data and physicians will continue to use the same chemotherapy cocktail as they did before.

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