Adjuvant therapy of Early Ovarian Cancer

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At diagnosis, approximately 30% of women with ovarian cancer have early-stage disease that is confined to the pelvis (FIG0 stage I and II). The prognosis of early-stage disease is better than that for stage III and IV disease, with 50-85 % of five year survival, but approximately 50% of women with early-stage ovarian cancer develop recurrent disease after surgery and may die from ovarian cancer. The primary and usually the only treatment for early-stage ovarian cancer has been surgery, which in theory could be curative in low-risk patients whose disease is limited to the ovaries. The relative importance of prognostic factors including tumor grade, histologic cell type, presence of ascitis, degree of tumor adherence, stage, state of capsule and DNA ploidy for defining individuals at low risk of recurrence is unknown[1,2]. Considerable subjectivity and lack of reproducibility of these factors have made practical utility very difficult but by and large it is widely accepted that suboptimal cyto-reduction, and grade of tumour are most important of them.

A number of therapies have been tried to attempt to improve survival in patients with early stage disease after their surgical debulking. Despite the fact that optimal staging and debulking is an important prognostic indicator the optimal cytoreducton is carried in not more than one third of patients. Apart from observation, investigated options of adjuvant therapy include intra-peritoneal radio-isotopes (P32), systemic chemotherapy and total abdominal and pelvic radiation therapy Many questions are yet to be answered and they include: single drug or combination, duration, indications and choice of drugs.

One of the earliest trials to address the role of adjuvant therapy in early ovarian cancer was GOG study conducted in 1970s by Hreschyshun et al[3]. Eighty six patients were randomized between observation, pelvic radiotherapy or oral melphalan. The study concluded that oral melphalan was better than pelvic radiotherapy though there was no difference was found in the groups. This study however showed a very significant difference in survival between the grade I tumours (90%) and poorly differentiated tumours (40-50%), emphasizing the need of adjuvant therapy in the latter group. Another trial by Young et al[4] emphasized that in stages Ia and Ib there was no benefit of adjuvant therapy, when they randomized between observation and oral melphalan. Same group in their second trial compared oral melphalan with single postop dose of 15 mci of intra-peritoneal P32 and had shown that in high grade and stage Ic and II adjuvant therapy with either of them was equally effective, though the risk of leukemia was higher in melphalan group.

Role of radiotherapy in early ovarian cancer has been extensively studied[5,6] and it was found to have survival benefit in high risk patients and when compared abdomino-pelvic radiotherapy was better than pelvic radiotherapy alone. Combination of pelvic radiotherapy and cyclophosphamide or chlorambucil was also found to have better survival than radiotherapy alone[6]. A Canadian trial compared all the three modalities of pelvic radiotherapy, oral melphalan, and radioactive phosphorus. The conclusions were that abdomino-pelivc radiotherapy was better than pelvic radiotherapy; oral melphalan was equal to radiotherapy or P32[7]. After advent of Cisplatin, its role was compared to adjuvant radiotherapy as well as radioactive phosphorus and found to be equally effective with less toxicity and adhesion related problems, hence was recommended as standard arm for future studies*.

However, no randomized trial has reliably demonstrated a survival advantage of any of these therapies over the others or over careful observation without immediate adjuvant therapy .The

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question of whether immediate adjuvant chemotherapy after surgery would prolong the time to recurrence and improve survival in patients with early-stage epithelial ovarian carcinoma was identified in 1990 by the Advanced Ovarian Cancer Trialists Group (AOCTG) as requiring investigation. In response, the International Collaborative Ovarian Neoplasm (ICON) collaborators initiated a randomized trial in 1991 of immediate adjuvant chemotherapy for early-stage ovarian cancer (ICON1). At the same time, the European Organisation for Research and Treatment of Cancer (EORTC) initiated a similar trial on Adjuvant Chemotherapy In Ovarian Neoplasm (ACTION). Early in the course of both trials, it was planned that a single independent data-monitoring committee would review the combined accumulating data from both the ICON1 and ACTION trials.

In ICON-I trial[9] 477 patients in 84 centers in five countries were randomly assigned to receive either adjuvant chemotherapy immediately following surgery (n = 241) or no adjuvant chemotherapy until clinically indicated (n = 236). Women who received adjuvant chemotherapy had better overall survival than women who did not (hazard ratio [HR] of 0.66, 95% confidence interval [CI] = 0.45 to 0.97; P = .03). Five-year survival figures were 70 % for women without adjuvant chemotherapy and 79% for women with adjuvant chemotherapy, a difference of 9% (95% CI = 1% to 15%). Adjuvant chemotherapy also improved recurrence-free survival (HR = 0.65; 95% CI = 0.46 to 0.91; P = .01) being 62% for women who did not receive adjuvant chemotherapy and 73% for women who received adjuvant chemotherapy, a difference of 11% (95% CI = 3% to 18%). Thus results of ICON-I trial suggest that platinum-based adjuvant chemotherapy improves survival and delays recurrence in patients with early-stage ovarian cancer.

In ACTION trial,[10] 448 patients from 40 centers in nine European countries were randomly assigned to either adjuvant platinum-based chemotherapy (n = 224) or observation (n = 224) following surgery. Endpoints were overall survival and recurrence-free survival, and the analysis was on an intention-to-treat basis. After a median follow-up of 5.5 years, the difference in overall survival between the two trial arms was not statistically significant (hazard ratio [HR] = 0.69, 95% confidence interval [CI] = 0.44 to 1.08; P = .lO). Recurrence-free survival, however, was statistically significantly improved in the adjuvant chemotherapy arm (HR = 0.63, 95% CI = 0.43 to 0.92; P = .02). Approximately one-third of patients (n = 151) had been optimally staged and two-thirds (n = 297) had not. Among patients in the observation arm, optimal staging was associated with a statistically significant improvement in overall and recurrence-free survival (HR = 2.31 [95% CI = 1.08 to 4.961; P = .03 and HR = 1.82 [95% CI = 1.02 to 3.241 P = .04, respectively). No such association was observed in the chemotherapy arm. In the non-optimally staged patients, adjuvant chemotherapy was associated with statistically significant improvements in overall and recurrence-free survival (HR = 1.75 [95% CI = 1.04 to 2.951; P = .03 and HR = 1.78 [95% CI = 1.15 to 2.771; P = .009, respectively). In the optimally staged patients, no benefit of adjuvant chemotherapy was seen. Adjuvant chemotherapy was associated with statistically significantly improved recurrence-free survival in patients with early-stage ovarian cancer. The benefit of adjuvant chemotherapy appeared to be limited to patients with non-optimal staging, i.e., patients with more risk of unappreciated residual disease.

A preplanned combined analysis of two parallel randomized clinical trials (ICON1 and ACTION]) in early stage ovarian cancer that compared platinum-based adjuvant chemotherapy with observation following surgery was carried out[11]. Between November 1990 and January 2000, 925 patients (477 in ICON1 and 448 in ACTION) who had surgery for early-stage ovarian cancer were randomly assigned to receive platinum-based adjuvant chemotherapy (n = 465) or observation (n = 460) until chemotherapy was indicated. After a median follow-up of over 4 years, 245 patients had died or had a recurrence (ICON1: 133, ACTION: 112). Overall survival at 5 years was 82% in the chemotherapy arm and 74% in the observation arm (difference = 8% [95% confidence interval (CI) = 2% to 12%]; hazard ratio [HR] = 0.67, 95% CI = 0.50 to 0.90; P = .008). Recurrence-free survival at 5 years was also better in the adjuvant chemotherapy arm than it was in the observation arm (76% versus 65%, difference = 11% [95% CI = 5%

to 16%]; HR = 0.64, 95% CI = 0.50 to 0.82; P = .001). Subgroup analyses provided no evidence of a difference in the size of effect of chemotherapy on survival in any pretreatment subcategory It was thus concluded that platinum-based adjuvant chemotherapy improved overall survival and recurrence- free survival at 5 years in this combined group of patients with early-stage ovarian cancer.

Early ovarian cancer has a varied prognosis de- Pending on the factors such as grade of the tumour optimal cytoreduction. It has been amply proven that there is no need for adjuvant therapy in Stage Ia and Ib with grade I tumours. In stage Ia and b with grade 2 or 3 tumours, stage II patients there is an advantage in overall and recurrence free survival when treated with 4 to 6 cycles of Cisplatin based chemotherapy This is very true if the cytoreduction is suboptimal. However, several questions are yet to be answered such as role of taxanes, number of cycles and optimal combination of chemotherapeutic agents, which may be addressed in future trials.

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