Cyclophosphamide Plus Cisplatin Versus Cyclophosphomide, Doxorubicin, and Cisplatin Chemotherapy of Ovarian Carcinoma: A Meta-Analysis

By the Ovarian Cancer Meta-Analysis Project*

Four randomized clinical trials comparing cyclophosphamide plus cisplatin (CP) versus cyclophosphamide, doxorubicin, and cisplatin (CAP) individually failed to show a significant survival difference in the treatment of ovarian carcinoma. However, by pooling 1,194 patients from these trials in a meta-analysis, there is a statistically significant survival benefit for CAP ($P = .02$); in addition, there is a significant advantage for CAP in frequency of negative second-look laparotomy (CAP, 30%; CP, 23%; $P = .01$). Because the dose intensity of CAP was greater than CP in three of the trials, it remains unresolved to what extent the benefit of CAP is from greater dose intensity and to what extent it is from the doxorubicin itself. Either interpretation suggests directions for improving the chemotherapy of ovarian carcinoma.

J Clin Oncol 9:1668-1674. © 1991 by American Society of Clinical Oncology.

IN RECENT YEARS, there has been intense interest in the chemotherapy of ovarian carcinoma, and several large-scale, randomized trials have been conducted of various drug combinations. These studies have frequently involved the use of cisplatin with cyclophosphamide and/or doxorubicin, but an optimal treatment regimen has not been established. Cisplatin is currently the most active agent in ovarian cancer (along with its analog, carboplatin), but the importance of other drugs is controversial. Five randomized trials have been published comparing cyclophosphamide plus cisplatin (CP) with doxorubicin (CAP) or without. These include trials of the Gynecologic Oncology Group (GOG),[1] the Gruppo Interegionale Cooperativo Oncologico Ginecologia (GICOG),[2] the Danish Ovarian Cancer Group (DACOVA),[3] the Gruppo Oncologico Nord-Ovest (GONO),[4] and a Hungarian study.[5] An unpublished trial of the German Cancer Study Group (GCSG) involved a similar comparison (U. Muller, personal communication, June 1990).

The GOG trial included patients with small-volume stage III disease; using dose schedules of CP and CAP with equal hematologic toxicity, this trial found no significant difference in progression-free interval, frequency of negative second-look laparotomy, or survival, although each parameter favored CAP slightly. In contrast to the GOG trial, the GICOG, DACOVA, and GONO trials simply added doxorubicin to CP in the CAP arm. (The GICOG study was actually a three-arm trial in stage III and IV cases, but the arms of interest here were CP and CAP.) Response rates, negative second-look rates, disease-free survival, and survival favored CAP but not significantly. The DACOVA trial also included patients with stage III and IV disease; there was no difference in negative second-look or survival rates, but as with the other trials, there was a slight advantage for CAP. The GONO trial included all stages; clinical response rates, survival, and progression-free survival favored CAP slightly, but the frequency of negative second-look favored CAP significantly ($P < .05$).

The Southeast European Oncology Group (SEEOG) study of CP (1,000/60 mg/m^2) and CAP (600/60/60 mg/m^2) was not available for further analysis[5]; the clinical response rates were 10 of 16 and 14 of 16, respectively. A significant survival advantage for CAP was reported, but the large

*Writing committee: George A. Omura (Gynecologic Oncology Group), Marc Buyse (Brussels), Silvia Marsoni (Gruppo Interegionale Cooperativo Oncologico Ginecologia), Kamma Bertelsen (Danish Ovarian Cancer Group), Pier Franco Conte (Gruppo Oncologico Nord-Ovest), Anders Jakobsen (Danish Ovarian Cancer Group), and Jan Vermorken (Amsterdam).

From the University of Alabama at Birmingham, Birmingham, AL; European Organization for Research and Treatment of Cancer Data Center, Brussels, Belgium; Istituto Di Ricerche Farmacologiche Mario Negri, Milan, Italy; Odense University Hospital, Odense, Denmark; Istituto Nazionale per la Ricerco Sul Cangro, Genoa, Italy; Aarhus University Hospital, Aarhus, Denmark; and Free University Hospital, Amsterdam, The Netherlands.

Submitted December 17, 1990; accepted March 6, 1991.

Address reprint requests to Marc Buyse, ScD, European Organization for Research and Treatment of Cancer Data Center, Avenue E. Mounier 83-B11, 1200 Brussels, Belgium.

0732-183X/91/0909-0005$3.00/0

imbalance with respect to performance status and the very small number of patients made the results of this study difficult to interpret.

Although none of these trials showed a convincing benefit for the addition of doxorubicin, the question arises as to whether the small differences noted might be real. This question has been addressed in the present report through a meta-analysis.

METHODS

Statistical Methods

All strictly randomized trials comparing CAP to CP (any schedule and/or dose) in advanced ovarian cancer were identified by searches in MEDLINE and Physician Data Query (PDQ) and from abstracts at conferences and personal contacts with the principal investigators. Six trials were identified, five of which had been published (Table 1).[1-5] Full details including the following data were obtained from the four larger trials (GICOG, GOG, DACOVA, GONO) on all individual patients, whether eligible or not and whether properly treated or not: baseline information (date of randomization, patient age at entry on trial, Eastern Cooperative Oncology Group/World Health Organization (ECOG/WHO) performance status, extent of residual disease, International Federation of Gynecology and Obstetrics stage, WHO histology and histologic grade, treatment assigned by randomization (CP or CAP), and follow-up information (clinical response, date of second-look operation, if any, pathologic response, date of relapse, and date of death or last visit). Each trial was checked extensively for imbalances between CAP and CP with respect to prognostic factors and duration of follow-up. No remarkable pattern or imbalance was noticed. Partial data with limited follow-up were also obtained from the two smaller trials (GCSG, SEEOG); however, these data could not be confirmed with the principal investigators. Therefore, the analyses herein are based chiefly on the four major trials. All analyses that could be performed using data from all six trials yielded results very similar to those obtained with the four major trials.

Survival times were analyzed using a stratified log-rank test. Proportions were analyzed using extensions of the Mantel-Haenszel method to combine data from several tables.[6] With these methods, the contribution of each trial to the overall result is proportional to the number of events in that trial. A Cox regression model was fitted on survival times to determine if the treatment effect remained significant after taking all known important covariates into account.[7]

Clinical Methods

Women with epithelial ovarian carcinomas of the usual cell types were eligible for all trials; borderline tumors (low malignant potential) were not eligible. Patients with prior irradiation or chemotherapy, second cancers, marrow or renal impairment, or cardiac or other medical conditions not suitable to receive chemotherapy were excluded. Differences in eligibility are shown in Table 2. Central randomization by telephone and randomization lists was used in all but the DACOVA study, in which separate randomization lists had been provided to the participating institutions.

A complete pathologic response was the disappearance of all lesions at second-look operation, negative peritoneal cytology, and multiple negative random biopsies after exploration of the entire abdominal cavity. The denominator for the pathologic complete response rate was the total number of patients randomized, regardless of whether a second-look operation could be performed.

Table 1 highlights the main differences between the trials with respect to treatment schedules and doses. Dose adjustments for the GOG, GICOG, and DACOVA trials are described in the original reports. In the GONO trial no dose modifications were called for, but re-treatment was delayed until hematologic recovery. Treatment policies after the trial period are also described in the original reports.[1-4]

The data presented in this report differ from those published on each individual study because all patients, not

Table 1. Trial Characteristics

Study	Accrual Years	Median Follow-Up (years)	Treatment	Dose (mg/m^2)	Time Interval (weeks)	No. of Courses	Total Accrual
GICOG[2]	1980-1986	6.5	CP	650/50	4	8	192
			CAP	650/50/50			190
GOG[1]	1981-1985	5.0	CP	1,000/50	3	6	213
			CAP	500/50/50			202
DACOVA[3]	1981-1984	5.5	CP	500/60	4	12	139
			CAP	500/40/60			136
GONO[4]	1982-1984	6.0	CP	600/50	4	6	63
			CAP	600/45/50			62
GCSG	1984-1987	3.5	CP	1,000/70	4	6	54
			CAP	500/30/70			42
SEEOG[5]	1984-1985	3.0	CP	1,000/60	3	10	16
			CAP	600/60/60			16
Total			CP				677
			CAP				648

Table 2. Main Eligibility Criteria

Study	Stage	Tumor Size (cm)	Age (years)
GICOG	III, IV	All	< 75
GOG	III	≤ 1	All
DACOVA	III, IV	All	< 70
GONO	IC to IV	All	18-74
GCSG	III, IV	All	< 70
SEEOG	III, IV	≥ 2	< 70

just the eligible patients, were included here, and follow-up was longer than in the original reports. The results presented below were confirmed by considering only eligible patients; in no case did the results materially change after exclusion of ineligible patients.

RESULTS

Figure 1 shows the survival curves for the individual trials including all patients; as in the original reports, the differences are not statistically significant. When the data from the GICOG, GOG, DACOVA, and GONO trials are combined, there is a statistically significant survival advantage for CAP (P = .02; Fig 2). The survival benefit is between 5% and 7% from year 2 to year 6. Overall, the odds ratio is 0.85, showing a 15% reduction in the odds of death in favor of CAP (Table 3). The overall negative second-look operation rate was 30% for CAP and 23% for CP (P = .01). This corresponds to an odds ratio of 1.39, showing a 39% increase in the odds of achieving a pathologic complete response through the use of CAP (Table 3). If cases with pathologic complete response are combined with microscopic residual disease (since microscopic disease might be missed at surgery in some "complete responses"), the overall percentages are 43% for CAP and 36% for CP (P = .01). None of the above results are qualitatively modified if the two smaller trials with partial data are included; the benefit of

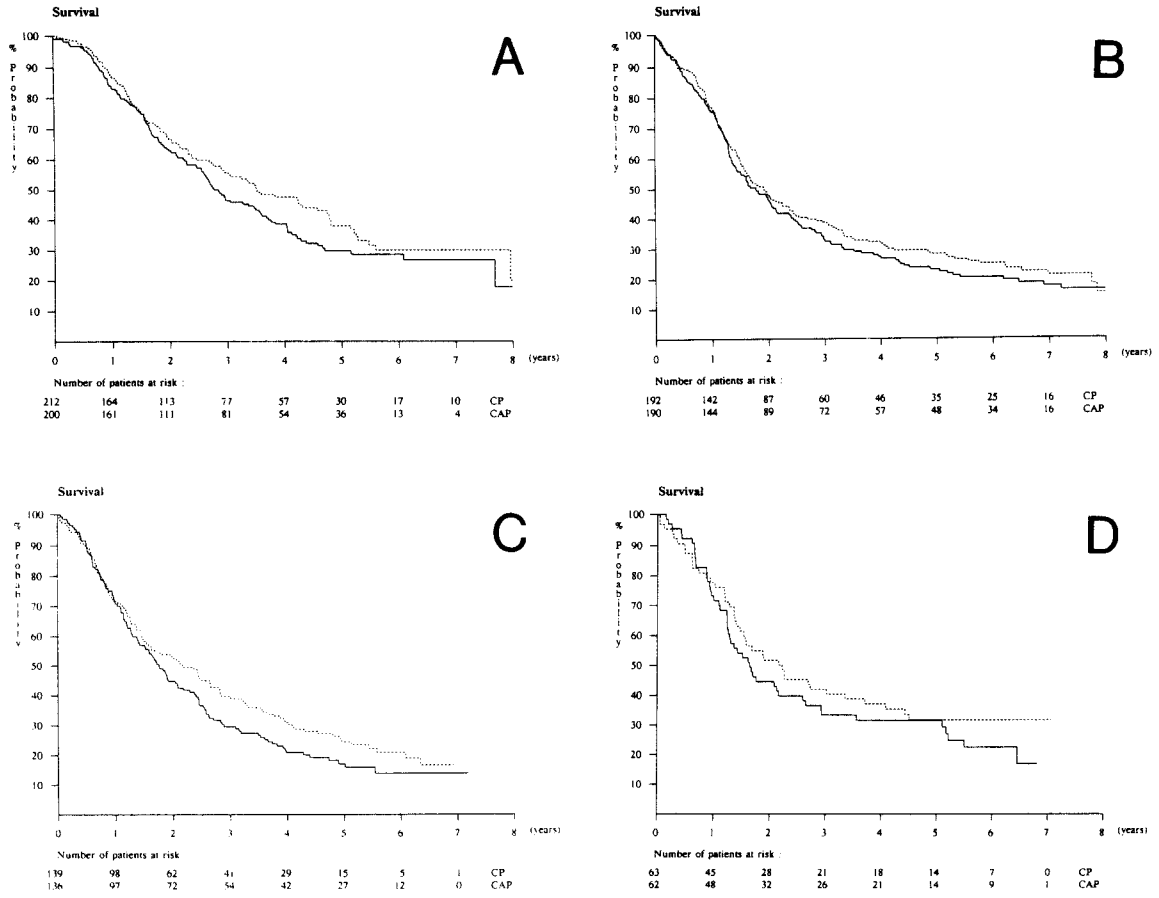

Fig 1. Survival curves of patients allocated to CP (—) and CAP (·····) in individual trials. Three patients were lost to follow-up at time 0 in the GOG trial (CP, one; CAP, two). N, total; O, dead. (A) GOG. CP: N 212, O 127; CAP: N 200, O 106; P = .17. (B) GICOG. CP: N 192, O 151; CAP: N 190, O 146; P = .39. (C) DACOVA. CP: N 139, O 116; CAP: N 136, O 107; P = .15. (D) GONO. CP: N 63, O 48; CAP: N 62, O 42; P = .33.

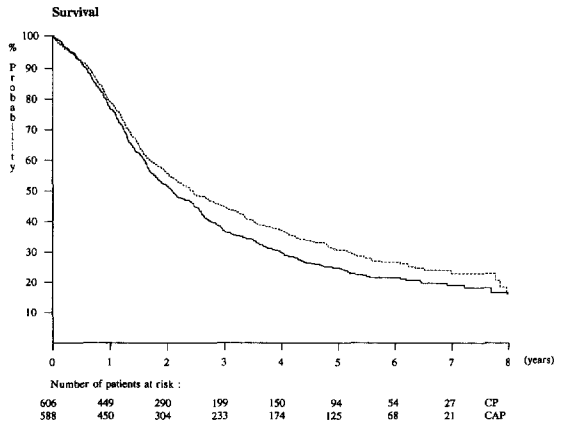

Fig 2. Overall survival curves (four trials) of patients allocated to CP (——; N, 606; O, 442) and to CAP (·····; N, 588; O, 401).

CAP persists in terms of survival ($P < .01$) and in terms of response ($P = .02$) (data not shown).

Several other factors were analyzed with respect to survival. Age $\leq$ 55 years, better performance status, smaller tumor volume, and grade I tumors (as opposed to grades II and III) were significantly favorable factors ($P < .0001$). Serous histology was favorable for survival compared with all other histologies ($P = .04$). In multivariate analysis, residual disease status ($P < .0001$), followed by performance status ($P < .0001$), age ($P < .0001$), treatment ($P = .012$), and stage ($P = .02$) were significant.

When this analysis was planned, there had been some speculation that doxorubicin might have a greater effect in bulky disease than in small-volume residual disease. However, the significant treatment effect was not greater in bulky disease and, if anything, it favored small-volume disease: the survival benefit of CAP over CP was largest in patients with no residual disease (odds ratio, 0.73) and smallest in patients with bulky disease (odds ratio, 0.91). Treatment effect was estimated and tested in all subsets defined by the known prognostic factors. There was no indication that treatment effect was qualitatively different in any subset or in any of the four studies.

DISCUSSION

By pooling the data on almost 1,200 patients from four chemotherapy trials in ovarian cancer, we have shown that a 7% difference in negative second-look operation rate and a 7% survival advantage at 6 years are statistically significant benefits of CAP compared with CP. This finding raises some questions: Is the benefit of CAP due to the doxorubicin, or is it a function of dose intensity? How can the information help improve the treatment of ovarian cancer? What are the limitations of meta-analysis as applied to such data?

Three of the studies added doxorubicin to fixed doses of CP. Thus, there was more toxicity; at the same time greater dose intensity was achieved. The dose of cyclophosphamide in those trials was modest (500 to 650 mg/m^2 every 4 weeks) and could certainly have been increased as an alternative to adding doxorubicin. That was done in the GOG trial, where CP 1,000/50 mg/m^2 was compared with CAP 500/50/50 mg/m^2, resulting in equal hematologic toxicity. The GOG results favored CAP slightly. Perhaps the trial should have

Table 3. Benefit

Study	CP Dead/Randomized	CAP Dead/Randomized	O – E	V	Odds Ratio	CI	P
Effect on overall survival							
GICOG	151/192	146/190	− 7.4	73.9	0.90	0.72-1.14	.39
GOG	127/213	106/202	− 10.5	58.2	0.83	0.65-1.08	.17
DACOVA	116/139	107/136	− 10.8	55.1	0.82	0.63-1.07	.15
GONO	48/63	42/62	− 4.6	22.4	0.82	0.54-1.23	.33
Overall	442/607	401/590	− 33.3	209.6	0.85	0.75-0.98	.02
Effect on PCR							
GICOG	41/192	48/190	3.7	17.1	1.24	0.77-2.00	.37
GOG	61/213	66/202	4.2	22.0	1.21	0.80-1.83	.37
DACOVA	26/139	36/136	5.3	12.0	1.56	0.89-2.74	.12
GONO	14/63	25/62	5.7	6.8	2.31	1.09-4.91	.03
Overall	142/607	175/590	18.9	57.9	1.39	1.07-1.79	.01

NOTE. Detailed calculations of the benefit of CAP over CP in terms of survival (top half) and PCR (bottom half). The odds ratio is estimated by exp [(O − E)/V], and its 95% CIs by exp [(O − E)/V ± 1.96/$\sqrt{V}$].[6]

Abbreviations: PCR, pathologic complete response; CI, confidence interval; O, observed number of events (top half, death; bottom half, PCR); E, expected number of events based on log-rank tables (top half) or 2 × 2 tables (bottom half); V, variance of O.

been larger, but the accrual requirements would have made it very difficult to plan and execute a trial in ovarian cancer looking for a 7% difference. In fact, a 15% increase in survival at 2 years was prospectively sought in the GOG trial, but the difference found in the meta-analysis was only 5% at 2 years and was even less in the GOG trial.

Is a 7% improvement clinically relevant? There are more than 45,000 new cases of ovarian cancer per year in the United States and Europe. All stages combined, the 5-year survival is no better than 30% to 40%. Thus, even if the true improvement was as small as 7%, several hundred women per year may benefit. Nevertheless, doxorubicin has side effects and toxicity that can be troublesome, such as chemical phlebitis, cellulitis, and cardiomyopathy, which may be life-threatening at higher doses. Could the same or better result be achieved with higher doses of cisplatin (at the expense of peripheral neuropathy and ototoxicity)? If a dose-response effect exists for cisplatin in ovarian cancer, high-dose cisplatin might overshadow any contribution of doxorubicin. This, clearly, is an open question requiring a reliable answer.

If the use of doxorubicin is responsible for the improved results, the current trend away from doxorubicin-containing regimens needs to be reconsidered. CAP as used in the four major trials is certainly not ideal. Substantially higher doses of doxorubicin could be used.[8] Better ways of using doxorubicin (and its analogs) in combination may exist.[9] On the other hand, if the advantage of CAP is from greater dose intensity, it supports many current efforts to further intensify treatment. The need remains, however, to use the most active drugs in optimal dose schedules, and not to assume that more drugs are better without validation with appropriate clinical trials.

The technique of meta-analysis used in this report is most useful when small treatment benefits are suspected, but individual trials lack the statistical power needed to identify these benefits.[10] Individual trials of small to moderate size are likely to yield false-negative results, and such results may detract from the use or further testing of an effective therapy. In the case at hand, the succession of four negative results may have wrongly suggested that doxorubicin had no role in the treatment of advanced ovarian cancer. It is erroneous to assume that meta-analyses are always statistically significant simply because the number of observations is so much larger than in individual trials; in cancer, some meta-analyses have been positive,[6] some negative,[11] and some equivocal.[12]

The present meta-analysis, based on full individual patient data makes optimal use of unbiased information. No approach based on partial published data is as reliable and as statistically efficient. The validity of our results might be jeopardized if other studies existed comparing CAP to CP, and if these studies had shown unfavorable results.[13] There is no evidence that such studies exist; therefore, the possibility that bias alone might explain our findings seems unlikely.

In addition to its sheer statistical power, meta-analysis is also useful to verify the claims made in the analysis of individual trials, particularly with respect to the effect of treatment among different subsets of patients. Such claims can often be explained solely by the play of chance.[14] For instance, in two of the trials at hand, the benefit of CAP in terms of response rate was reported to be seen only in patients with more than 2 cm residual disease after surgery.[2,4] In an interim analysis of the DACOVA trial,[15] the benefit in response rate was reported to be seen mostly in patients with serous and undifferentiated tumors. Thus, it had been hypothesized that the benefit of CAP, if any, would be limited to the more advanced tumors, particularly those with a large initial tumor bulk and/or poorly differentiated histologic features. The present meta-analysis failed to confirm this hypothesis; in fact, it showed a remarkably consistent benefit, albeit small, of CAP throughout all subsets, all studies, and all the end points analyzed.

Finally, it should be mentioned that another meta-analysis in ovarian cancer is currently underway with the sponsorship of the British Medical Research Council[16] to compare single-agent chemotherapy with combinations, etc. These two efforts are independent of each other but will, we believe, be complementary rather than duplicative.

ACKNOWLEDGMENT

The authors thank the GOG, GICOG, DACOVA, and GONO for making data from the individual trials available for analysis (see Appendix for participating institutions), Dr U. Muller for providing data on the GCSG trial, and the Farmitalia Carlo Erba Company for financial support for the project.

APPENDIX

The following individuals, groups, and institutions participated in the studies discussed in this report:

Gynecologic Oncology Group: University of Alabama at Birmingham, Birmingham, AL; Oregon Health Sciences University, Portland, OR; Duke University Medical Center, Durham, NC; Temple University Health Science Center Hospital, Philadelphia, PA; University of Rochester Medical Center, Rochester, NY; Walter Reed Army Medical Center, Washington, DC; University of Minnesota Medical School, Minneapolis, MN; University of Southern California Medical Center at Los Angeles, Los Angeles, CA; University of Mississippi Medical Center, Jackson, MS; Colorado Foundation for Medical Care, Denver, CO; University of California Medical Center at Los Angeles, Los Angeles, CA; The Milton S. Hershey School of Medicine of Pennsylvania State University, Hershey, PA; Georgetown University Hospital, Washington, DC; University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; University of Iowa Hospitals and Clinics, Iowa City, IA; University of Texas Health Science Center at Dallas, Dallas, TX; Indiana University Medical Center, Indiannapolis, IN; Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC; The Albany Medical College of Union University, Albany, NY; University of California Medical Center at Irvine, Irvine, CA; Tufts New England Medical Center, Boston, MA; Illinois Cancer Council, Chicago, IL; University of Pittsburgh School of Medicine, Pittsburgh, PA; St. Louis University Medical Center, St. Louis, MO; State University of New York Downstate Medical Center, Brooklyn, NY; Latter Day Saints Hospital, Salt Lake City, UT; Eastern Virginia Medical School, Norfolk, VA; Cleveland Clinic Foundation, Cleveland, OH; University of Utah Medical Center, Salt Lake City, UT; University of Connecticut Medical Center, Farmington, CT; University of Michigan Medical School, Ann Arbor, MI; University of Puerto Rico, School of Medicine, San Juan, Puerto Rico; Jacksonville University Hospital, Jacksonville, FL; and University of New Mexico Cancer Research and Treatment Center, Albuquerque, NM.

Gruppo Interegionale Cooperativo Oncologico Ginecologia: G. Bolis, President, University of Milan, Melloni; S. Marsoni, Istituto di Ricerche Farmacologiche Mario Negri, Milan; C. Belloni, University of Milan; U. Bianchi, University of Brescia; P.F. Bolis, University of Pavia; G. Bortolozzi, University of Milan; N. Colombo and A. Epis, University of Milan, Monza; G. Giardina, University of Turin; N. Natale, University of Milan, Sacco; S. Pecorelli, University of Brescia; U. Redaelli, Ospedale S. Paolo, Milan; M. Santoiemma, University of Ferrara; M.G. Valsecchi, Istituto di Biometria, University of Milan; L. Vassena, University of Milan, Monza; F. Vergadoro, University of Milan, Melloni; and C. Mangioni, University of Milan, Monza, Italy.

Danish Ovarian Cancer Group: Odense University Hospital, Odense; Herlev Hospital, Herlev; Aalborg Hospital, Aalborg; and Arhus University Hospital, Arhus, Denmark.

Gruppo Oncologico Nord-Ovest: R. Rosso, Instituto Nazionale Ricerca Cancro, Genova; C. Mossetti, Ospedale S. Anna, Torino; A. Cabrioti, Istituto Oncologia, Ospedale S. Giovanni, Torino; M. Centonza, Ospedale S. Martino, Genova; S. Rugiati, Ospedale S. Paolo, Savona; Ospedale S. Lazzaro, Alba; A. Storace, Ospedale Galliera, Genova; M. Messineo and C. Bernardini, Ospedale S. Bartolomeo, Sarzana; F. Misurale, Ospedale Civile, Rapallo; Ospedale Civile, Sampierdarena; and the Clinica Ostetrica Ginecologica Universita, Genova, Italy.

REFERENCES

1. Omura GA, Bundy BN, Berek JS, et al: Randomized trial of cyclophosphamide plus cisplatin with or without doxorubicin in ovarian carcinoma: A Gynecologic Oncology Group study. J Clin Oncol 7:457-465, 1989

2. Gruppo Interegionale Cooperativo Oncologico Ginecologia: Randomized comparison of cisplatin with cyclophosphamide/cisplatin and with cyclophosphamide/doxorubicin/cisplatin in advanced ovarian cancer. Lancet 2:353-359, 1987

3. Bertelsen K, Jakobsen A, Andersen JE, et al: A randomized study of cyclophosphamide and cisplatinum with or without doxorubicin in advanced ovarian carcinoma. Gynecol Oncol 28:161-169, 1987

4. Conte PF, Bruzzone M, Chiara S, et al: A randomized trial comparing cisplatin plus cyclophosphamide versus cisplatin, doxorubicin and cyclophosphamide in advanced ovarian cancer. J Clin Oncol 4:965-971, 1986

5. Hernadi Z, Juhashz B, Poka R, et al: Randomized trial comparing combinations of cyclophosphamide and cisplatinum without or with doxorubicin or 4-epi-doxorubicin in the treatment of advanced ovarian cancer. Int J Gynecol Obstet 27:199-204, 1988

6. Early Breast Cancer Trialists Collaborative Group: The effects of tamoxifen and of cytotoxic therapy on mortality in early breast cancer: An overview of 61 randomized trials among 28,896 women. N Engl J Med 319:1681-1692, 1988

7. Cox DR: Regression models and life tables [with discussion]. J R Stat Soc [B] 30:248-275, 1972

8. Wheeler R, Ensminger WD, Thrall JH, et al: High-dose doxorubicin: An exploration of the dose response curve in human neoplasia. Cancer Treat Rep 66:493-498, 1982

9. Levi F, Benavides M, Chevelle C, et al: Chemotherapy of advanced ovarian cancer with tetrahydropyranyl doxorubicin and cisplatin: A randomized phase II trial with an evaluation of circadian timing and dose intensity. J Clin Oncol 8:705-714, 1990

10. Collins R, Gray R, Godwin J, et al: Avoidance of large biases and large random errors in the assessment of moderate treatment effects: The need for systematic overviews. Stat Med 6:245-250, 1987

11. Stell PM, Rawson NSB: Adjuvant chemotherapy in head and neck cancer. Br J Cancer 61:779-787, 1990

12. Buyse M, Zeleniuch-Jacquotte A, Chalmers TC: Adjuvant therapy of colorectal cancer: Why we still don't know. JAMA 259:3571-3578, 1988

13. Simes RJ: Publication bias: The case for an interna-

tional registry of clinical trials. J Clin Oncol 4:1529-1541, 1986

14. Buyse M: Analysis of clinical trial outcomes: Some comments on subgroup analyses. Controlled Clin Trials 10:187S-194S, 1990 (suppl)

15. Jakobsen A, Bertelsen K, Sell A, et al: Advantage of CAP over CP in terms of survival in advanced ovarian carcinoma. Proc Am Soc Clin Oncol 4:113, 1985 (abstr C440)

16. MRC Gynaecological Cancer Working Party: Guest editorial: An overview in the treatment of advanced ovarian cancer. Br J Cancer 61:495-496, 1990