Chemotherapy in advanced ovarian cancer: an overview of randomised clinical trials

Advanced Ovarian Cancer Trialists Group

Abstract

***Objectives*—To consider the role of platinum and the relative merits of single agent and combination chemotherapy in the treatment of advanced ovarian cancer.**

***Design*—Formal quantitative overview using updated individual patient data from all available randomised trials (published and unpublished).**

***Subjects*—8139 patients (6408 deaths) included in 45 different trials.**

***Results*—No firm conclusions could be reached. Nevertheless, the results suggest that in terms of survival immediate platinum based treatment was better than non-platinum regimens (overall relative risk 0·93; 95% confidence interval 0·83 to 1·05); platinum in combination was better than single agent platinum when used in the same dose (overall relative risk 0·85; 0·72 to 1·00); and cisplatin and carboplatin were equally effective (overall relative risk 1·05; 0·94 to 1·18).**

***Conclusions*—In the past, randomised clinical trials of chemotherapy in advanced ovarian cancer have been much too small to detect the degree of benefit which this overview suggests is realistic for currently available chemotherapeutic regimens. Hence a new trial comparing cisplatin, doxorubicin, and cyclophosphamide (CAP) with carboplatin has been launched and plans to accrue 2000 patients.**

Introduction

Ovarian carcinoma is the seventh most common cancer of women in the world. Some 140 000 new cases are diagnosed every year and the disease is responsible for the greatest number of deaths from gynaecological malignancy in Europe and North America.[1] Despite over 50 randomised clinical trials having examined the relative efficacy of different chemotherapeutic regimens in advanced disease (FIGO (International Federation of Gynaecology and Obstetrics) stages III and IV), individually these trials have been too small to show clear benefit of one type of chemotherapy over another. Nevertheless, many of these trials have had an important influence on clinical practice, and consequently the type and intensity of chemotherapy used routinely for patients with advanced disease have fluctuated greatly.

Ovarian cancer was one of the first solid malignant tumours to be treated by chemotherapy, and the single alkylating agents that were first used over 30 years ago were considered optimal treatment until the mid-1970s. The past 15 years, however, have seen many changes in disease management. In 1978 a small randomised trial in advanced disease found that Hexa-CAF, a combination of cytotoxic drugs (hexamethylmelamine, cyclophosphamide, methotrexate, and fluorouracil), achieved higher response rates than the single alkylating agent melphalan and suggested the possibility of a corresponding improvement in survival.[2] At about the same time phase II studies suggested that cisplatin was the most promising new drug then available.[3] These results rapidly led to the standard use of cisplatin in combination with other cytotoxic drugs, usually doxorubicin and cyclophosphamide with or without hexamethylmelamine.[4,5]

When, however, doubt was cast on the effectiveness of doxorubicin by both randomised phase III trials[6-8] and phase II studies in patients not responding to cisplatin[9] several major centres adopted cisplatin plus cyclophosphamide as standard. Furthermore, when other trials failed to find significant survival differences between single agent cisplatin and cisplatin in combination with other drugs[10,11] some centres reverted to using single agent platinum as routine first line treatment. Recently a large number of trials have compared cisplatin with its less nephrotoxic and neurotoxic analogue carboplatin, and although follow up times were often short, many institutions have now adopted carboplatin as standard.

Currently it is unclear what constitutes optimal chemotherapy for advanced disease and treatment strategies vary both nationally and internationally. What is clear is that to date no individual clinical trial has been large enough to detect survival differences of the magnitude that could reasonably be expected with available treatment.[12] Consequently the inconclusive results of over 50 such trials reported could be consistent with moderate treatment benefits.[13] The British Medical Research Council Gynaecological Cancer Working Party realised the need to synthesise the information from these trials to evaluate currently used chemotherapeutic regimens. Given the problems associated with a qualitative review of published work,[13] this group initiated an overview which used formal quantitative methods to combine the results from all available randomised trials examining the role of platinum and of combination chemotherapy in the treatment of advanced ovarian cancer. At the outset the MRC overview secretariat contacted the investigators responsible for each trial, inviting their collaboration. In so doing it established the Advanced Ovarian Cancer Trialists Group, under whose auspices the overview was conducted.

Methods and data

The relative merits of single agent and combination chemotherapy and the role of platinum in disease management were sought, and five comparisons between different forms of chemotherapy were identified as being of interest. These were: (I) single non-platinum agent versus non-platinum combination; (II) single non-platinum agent versus platinum combination; (III) addition of platinum to a regimen; (IV) single agent platinum versus platinum combination; (V) cisplatin versus carboplatin.

Trials were eligible for inclusion in the overview if they examined first line treatment for advanced epithelial ovarian carcinoma and made one or more of the comparisons listed above. Each had also to be unconfounded and believed to have been randomised in a manner that precluded prior knowledge of the next treatment assignment. To avoid publication bias[14] it was essential that both published and unpublished studies were included, and various methods were employed to identify relevant trials. A bibliographic

Advanced Ovarian Cancer Trialists Group
Members of the trialists group and the organisations and groups that collaborated in the overview are listed at the end of this report.

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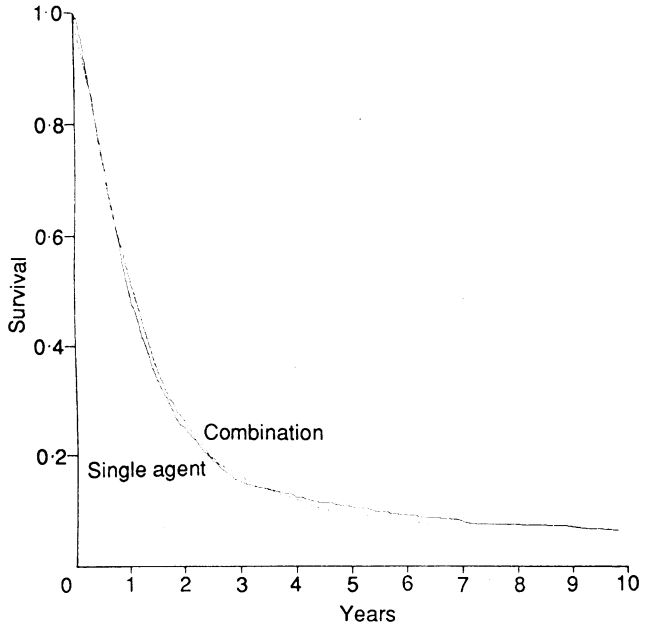

	Numbers at risk										
Single non-platinum agent	1379	649	315	185	152	126	104	90	76	66	50
Non-platinum combination	1767	893	427	258	182	138	116	94	82	70	61

FIG 1—*Survival curves for comparison I (single non-platinum agent v non-platinum combination)*

review by means of MEDLINE, CancerLit, and published texts was carried out. This was supplemented by examining the trial registers produced by the National Cancer Institute (PDQ ClinProt) and the United Kingdom Co-ordinating Committee on Cancer Research.[15] The proceedings of relevant clinical meetings were also consulted. In addition, questionnaires were sent to the principal authors of published trials and to international members of the Royal College of Obstetricians and Gynaecologists asking them to supplement a provisional list of trials. Pharmaceutical companies concerned in ovarian cancer treatment were also approached in this way.

Fifty three eligible randomised trials were identified, two other potentially eligible studies having to be excluded on the ground that they did not seem to be appropriately randomised. At the time of data collection for the overview roughly 30% of these eligible trials had not been published fully. Information was available from the 45 studies listed in appendix A[6 8 10 11 16-50] (unpublished references (A)-(F)) and unavailable from the eight eligible trials listed in appendix B.[2 51-59] Information was sought for each individual patient randomised in these studies, and the 45 available trials included data on 8139 patients (6408 deaths) originating from 11 different countries. These patients accounted for 95% of all known patients entered into randomised clinical trials of chemotherapy in advanced ovarian carcinoma that met the overview criteria for eligibility.

In all but two cases the individual patient information that was supplied for studies was updated for the overview. Thus the overview used information from an extended period with, for example, a median follow up of 10 years in trials comparing non-platinum single agents with non-platinum combinations. Incoming data were checked for any obvious flaws or inconsistencies such as missing values, dates out of sequence, and apparent differences between the data set and publication. Problems were rectified by correspondence with the principal investigator. In order to avoid the potential bias of exclusion after randomisation it was necessary to recover data from patients who had been randomised but excluded from the analysis of individual trials. Virtually all of this information was recovered, so that 99·5% of all patients randomised in the studies included in the overview were available for analysis. After collection, processing, and checking of the data individual trialists were sent a printout of their data set as stored in the overview database together with calculated survival curves so that they could check for errors.

All analyses were carried out on an intention to treat basis, patients being analysed according to their allocated treatment irrespective of whether they actually received that treatment. For each comparison survival analyses were stratified across all trials to generate log rank statistics. The individual observed and expected numbers of deaths as calculated in these actuarial survival analyses were pooled to provide an overall relative risk for the relevant comparison. This value gives the relative risk of death associated with two types of treatment. For example, when comparing treatment A with treatment B a relative risk of 0·8 represents a 20% decrease in the risk of death when using treatment A whereas a value of 1·2 represents a 20% increase in the relative risk of death when using treatment A. A relative risk of unity represents no difference in the risk of death associated with the two treatments. Appendix C explains the graphical displays used in the figures to present the relative risks for the various trials.

All p values are two sided, and the χ^2 values were calculated on one degree of freedom unless otherwise specified.

Results

Table I summarises the numbers of patients and deaths in comparisons I-V.

TABLE I—*Numbers of trials, deaths, and patients per comparison*

Comparison	No of available trials	No of unavailable trials	No of deaths	No of patients
I	16	6	2817	3146
II	11	2	1136	1329
III	8	0	1134	1408
IV	6	0	712	925
V	11	0	1771	2061
Total*	45	8	6408	8139

*Total numbers of trials, deaths, and patients are not simple sum of those given for comparisons I-V. Some trials were included in two comparisons but counted only once in totals.

COMPARISON I: SINGLE NON-PLATINUM AGENT VERSUS NON-PLATINUM COMBINATION

For comparison I data were available from 16 of 22 eligible trials, comprising 1379 patients randomised to receive a single non-platinum agent and 1767 to receive non-platinum combinations[6 16-28] (unpublished reference (A)). The reason for the imbalance in numbers was that some trials used two or more combination arms. A total of 2817 deaths were observed and the median duration of follow up was 10 years. Figures 1 and 2 show the results. There was no evidence of any overall difference between the two types of treatment (χ^2=0·65; p=0·42), the overall relative risk being 0·98 (95% confidence interval 0·91 to 1·05). This equivalence is apparent in figure 2, which shows a seemingly random scatter of relative risk values, 10 trials favouring combination chemotherapy, seven favouring the single agent, and two favouring neither. With the exception of a single trial which indicated a significant improvement in survival with combination chemotherapy all the trials yielded confidence intervals straddling unity, indicating their inconclusive outcome.

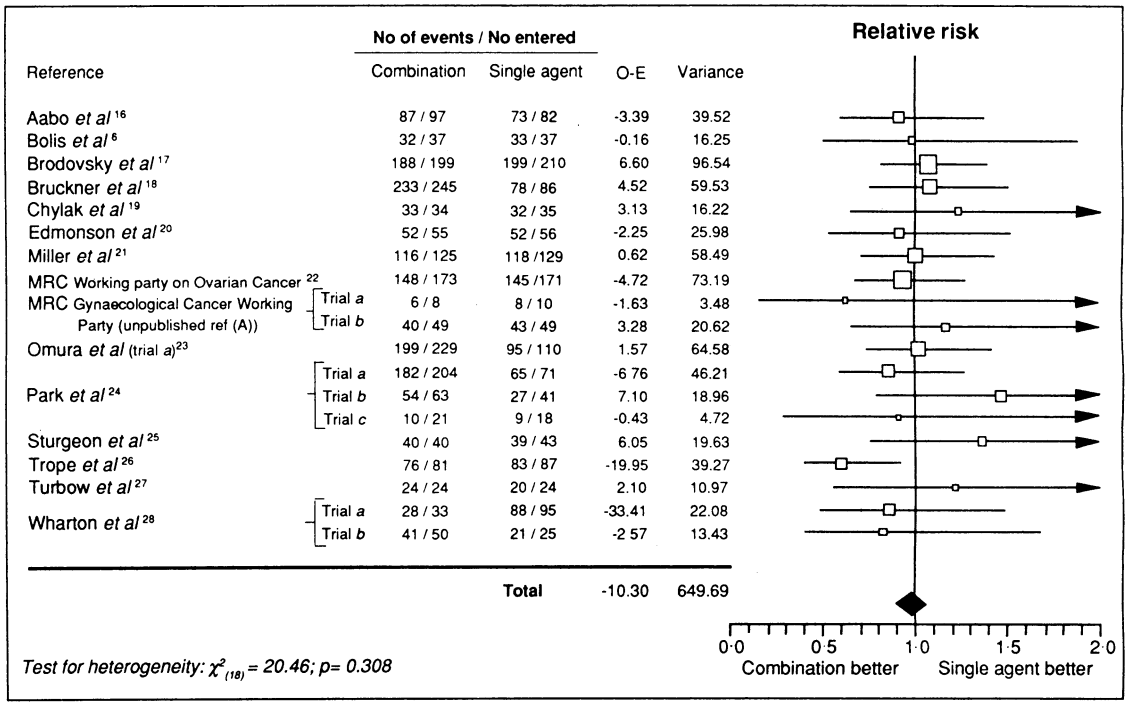

FIG 2—*Relative risks for comparison I. (O−E=Observed minus expected. Negative value indicates that treatment group fared better than controls. Trials making more than one comparison of interest (that is, with multiple treatment arms) are labelled a, b, etc. Open squares represent relative risks in trials. Sizes of symbols are directly proportional to amount of information in trials. Bars are 99% confidence intervals. Occluded lozenge represents pooled total relative risk and 95% confidence interval. See appendix C for full explanation of graphical displays of relative risk)*

TABLE II—*Doses of cisplatin used in combination in comparison II*

Cisplatin dose (mg/m²)	No of trials using dose	No of patients in trials using dose
30	1	80
40	1	11
50	6	940
75	1	100
80	1	89
100	1	109

COMPARISON II: SINGLE NON-PLATINUM AGENT VERSUS PLATINUM COMBINATION

Comparison II contained 13 eligible trials[25 29-36 58 59] (unpublished references (A), (B)), of which data were available from 11. In these trials 659 patients were randomised to receive a single non-platinum drug and 670 to receive a platinum combination, although many of the patients allocated to the single agent received platinum on relapse. The median follow up period was 6·5 years and the total number of observed deaths 1136. The dose of cisplatin used in the combination arm of these trials ranged from 30 to 100 mg/m², 50 mg/m² being used in six trials (table II). The survival curves (fig 3) showed an initial separation between the two treatments, although the curves had converged by year 6. There was no overall significant difference between the two treatments (χ^2=1·09; p=0·30), the overall relative risk being 0·93 (95% confidence interval 0·83 to 1·05) (fig 4). There was no obvious relation between the dose of cisplatin used and the estimate of the treatment difference (fig 4). Nevertheless, the pattern seemed to favour the combinations, most of the relative risk values lying to the left of unity (fig 4).

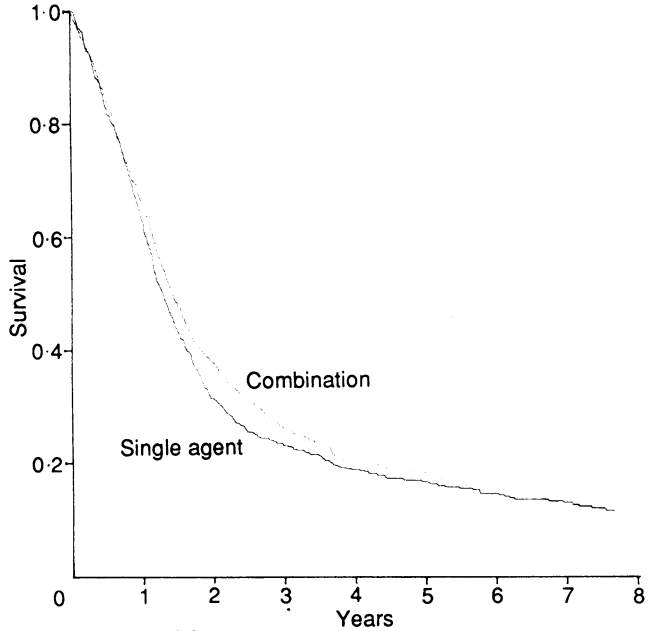

FIG 3—*Survival curves for comparison II (single non-platinum agent v platinum combination).*

COMPARISON III: ADDITION OF PLATINUM TO A REGIMEN

Data were available from all eight trials eligible for comparison III[31 33 34 37 38] (unpublished references (A)-(C)), which examined the effect of adding platinum to either a single drug or a drug combination. As five trials compared a single alkylating agent with the same alkylating agent plus cisplatin, these trials were eligible for inclusion in comparisons II and III. Data from these five trials were therefore common to both this and comparison II.

A total of 712 patients were randomised to the non-platinum arms and 696 to receive the platinum combinations. The median follow up period was six years, and a total of 1134 deaths were observed. The dose of cisplatin used in these studies showed less variation than in comparison II, ranging from 40 to 80 mg/m², five trials using 50 mg/m². The survival curves (fig 5) were similar to those in comparison II (fig 3), an early trend favouring the cisplatin combination up to about year 6. The overall difference between the two curves was, however, not significant (χ^2=2·8; p=0·1). The pooled relative risk of 0·91 (95% confidence interval 0·81 to 1·02) also favoured the platinum combination (fig 6). There was no obvious correlation between the dose of cisplatin used and the estimate of the treatment difference.

COMPARISON IV: SINGLE AGENT PLATINUM VERSUS PLATINUM COMBINATION

Data from all six trials eligible for comparison IV were available[10 11 39 40] (unpublished references (D), (E)), five of these trials using cisplatin and one (unpublished reference (E)) using carboplatin. The imbalance in the numbers of patients randomised—

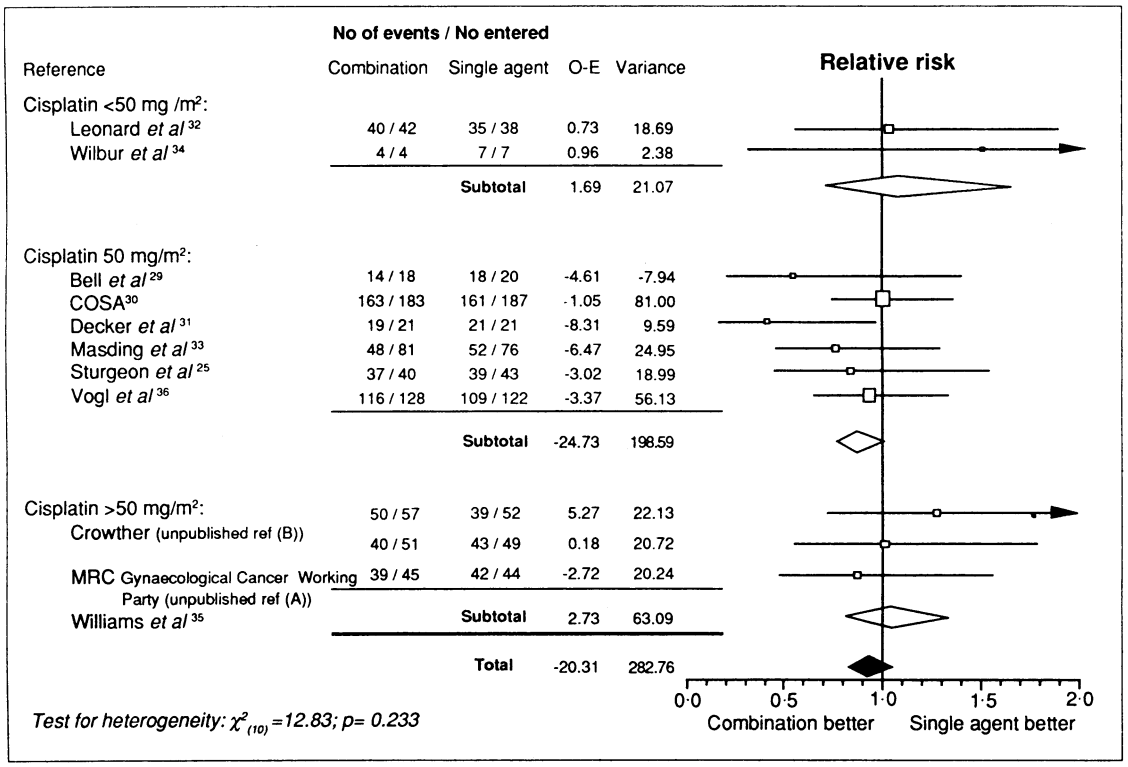

FIG 4—*Relative risks for comparison II. (Open lozenges represent pooled sub-total relative risks and 95% confidence intervals. Other details as in legend to fig 2 and appendix C)*

TABLE III—*Doses of platinum used in comparison V*

Cisplatin dose (mg/m²)	Carbo-platin dose (mg/m²)	No of trials using dose	No of patients in trials using dose
	Single agent		
100	400	3	392
	Combination		
20	350	1	335
50	200	1	165
50	250	1	51
60	150	1	104
75	300	1	447
80	350	1	173
100	300	2	394

360 to single agent platinum, 565 to platinum combinations—was due to the three arm GICOG study (Gruppo Interegionale Cooperativo Oncologico Ginecologia)[10] having utilised two different platinum combinations. A large proportion of patients in comparison IV (60%) were from that trial. A total of 712 deaths were observed, and the median follow up period was 6·5 years. One trial[40] had a slightly different objective from the others, in that it compared high dose cisplatin (100 mg/m²) given as a single agent with low dose cisplatin (20 mg/m²) given in combination. In all other trials in comparison IV the dose of platinum was about equal in both arms and the dose of cisplatin did not exceed 60 mg/m². The analysis in comparison IV was therefore performed both including and excluding that trial.

All trials—The survival curves (fig 7) suggested a difference in favour of the combination chemotherapy after two years, which was maintained until about year 8. The overall difference between the curves was not significant (χ^2=2·53; p=0·11). Likewise, the overall relative risk of 0·89 had a confidence interval straddling unity (95% confidence interval 0·76 to 1·04) (fig 8).

Excluding high dose-low dose study—After excluding the high dose-low dose study the difference between the two curves achieved borderline significance (χ^2=4·82; p=0·03), and the overall relative risk of 0·85 (95% confidence interval 0·72 to 1·00) (fig 8) suggested a 15% reduction in the risk of death in favour of the platinum combination.

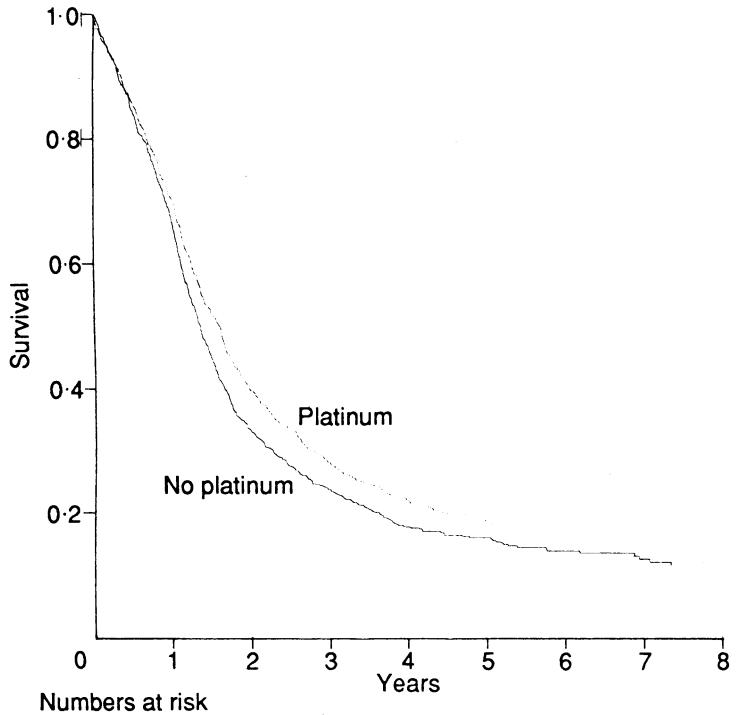

FIG 5—*Survival curves for comparison III (non-platinum regimen v same regimen plus plantinum)*

COMPARISON V: CISPLATIN VERSUS CARBOPLATIN

Comparison V included trials comparing carboplatin with cisplatin either as single agents or in combination with other drugs. Data were available from all 11 eligible trials[41-50] (unpublished reference (F)), in which 1023 patients were randomised to receive cisplatin and 1038 to receive carboplatin. The total number of observed deaths was 1771, and a median follow up of only three years reflected the comparative recency of these trials. Table III gives the doses of platinum used. The survival curves (fig 9) showed no significant difference in overall survival between the two treatments (χ^2=0·91; p=0·34), and this was reflected in an overall relative risk of 1·05 (95% confidence interval 0·94 to 1·18) (fig 10). There was no apparent relation between the estimate of treatment difference and whether single agents or combinations of cisplatin and carboplatin were compared. No individual study indicated significant benefit for either treatment (fig 10).

Discussion

In sharp contrast to the curative potential of chemotherapy in some cancers—for example, testicular

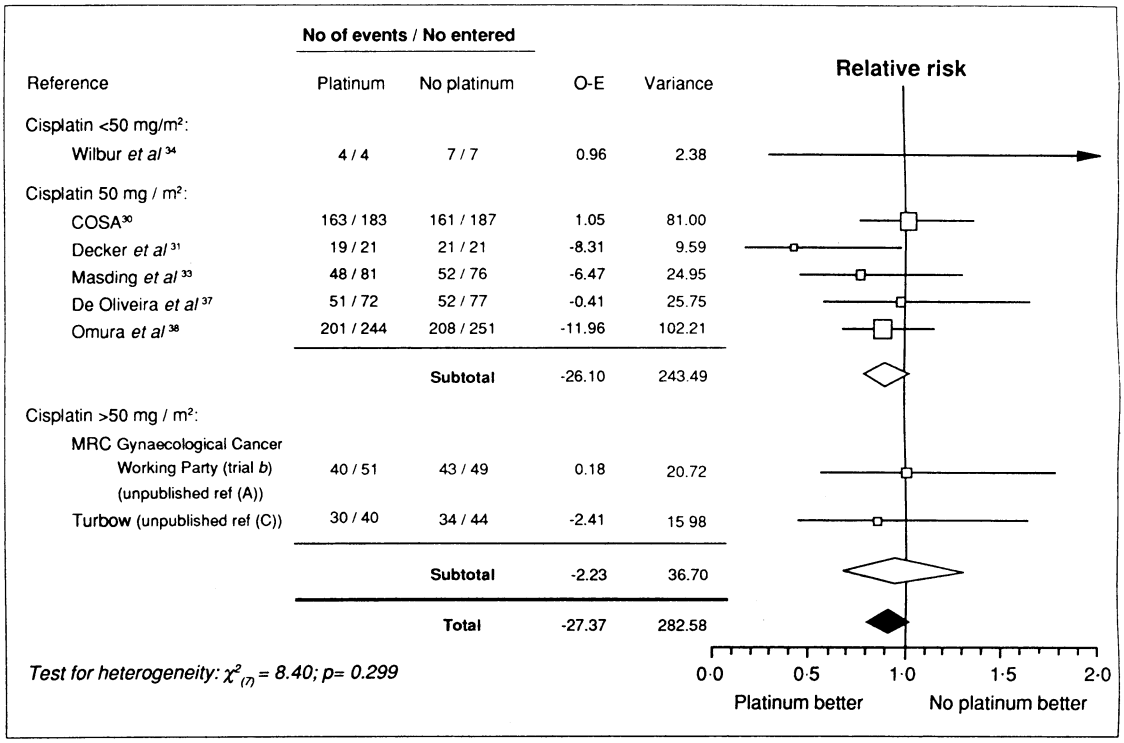

FIG 6—*Relative risks for comparison III. (Details as in legends to figs 2 and 4 and appendix C)*

teratoma—plainly chemotherapy has not yet achieved a substantial improvement in survival in patients with advanced ovarian carcinoma. Moderate benefits may have been gained, however, which—though possibly not dramatic given the incidence of the disease—may be extremely important to public health. To detect any such moderate improvements in survival in the comparisons of interest this overview presents the collation and analysis of updated individual information on over 8000 patients from 45 trials in 11 countries.

The lack of randomised trials including an untreated control group did not permit an analysis of the role of chemotherapy in its own right. In addition, the wide variety of drug treatments tested did not permit analyses of individual regimens but led to trials being grouped according to the type of drugs that they compared. The comparison of single non-platinum agents with non-platinum combinations (comparison I) included trials that were reported over roughly 10 years, mainly during the 1970s. Consequently, not only were the treatment regimens that were grouped together rather heterogeneous but the dose and scheduling of drugs also varied a good deal. Some of the treatments that were being tested in those trials might be considered ineffective today. Given these limitations, this overview offers no clear evidence that non-platinum drug combinations are superior to non-platinum single agents.

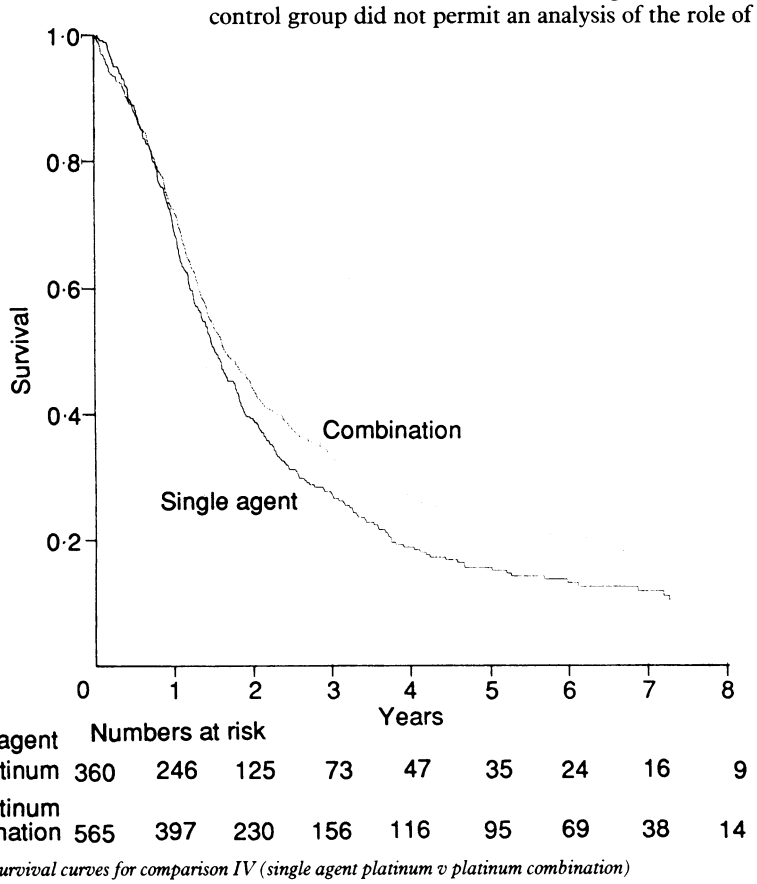

FIG 7—*Survival curves for comparison IV (single agent platinum v platinum combination)*

The comparison of single non-platinum agents with platinum combinations (comparison II) might be expected to have shown the largest treatment effect as it was comparing what is often thought of as the least intensive form of treatment with the most intensive. There was no significant difference between the two types of treatment. Of these trials, one compared the sequential versus combined use of chlorambucil and cisplatin,[30] and only one of the remainder (unpublished reference (B)) did not allow the use of cisplatin on relapse for those patients allocated to receive a single non-platinum agent. Many of the patients therefore received some form of platinum based treatment. Thus the comparison may have been examining immediate versus delayed platinum treatment. The dose of platinum used in the combination arm varied, but more than half of the studies used 50 mg/m².

The dose of cisplatin used in trials examining the addition of platinum to a regimen (comparison III) was more homogeneous, and any additional drugs were common to both arms. This was therefore a somewhat cleaner comparison. Results were similar to those in comparison II, an early trend favouring the platinum based regimen being lost over time. The similarity was not surprising as several trials were common to both these comparisons and there were the same problems associated with patients allocated non-platinum treatment receiving cisplatin on relapse. Figures 4 and 6 illustrate a pattern favouring the platinum combina-

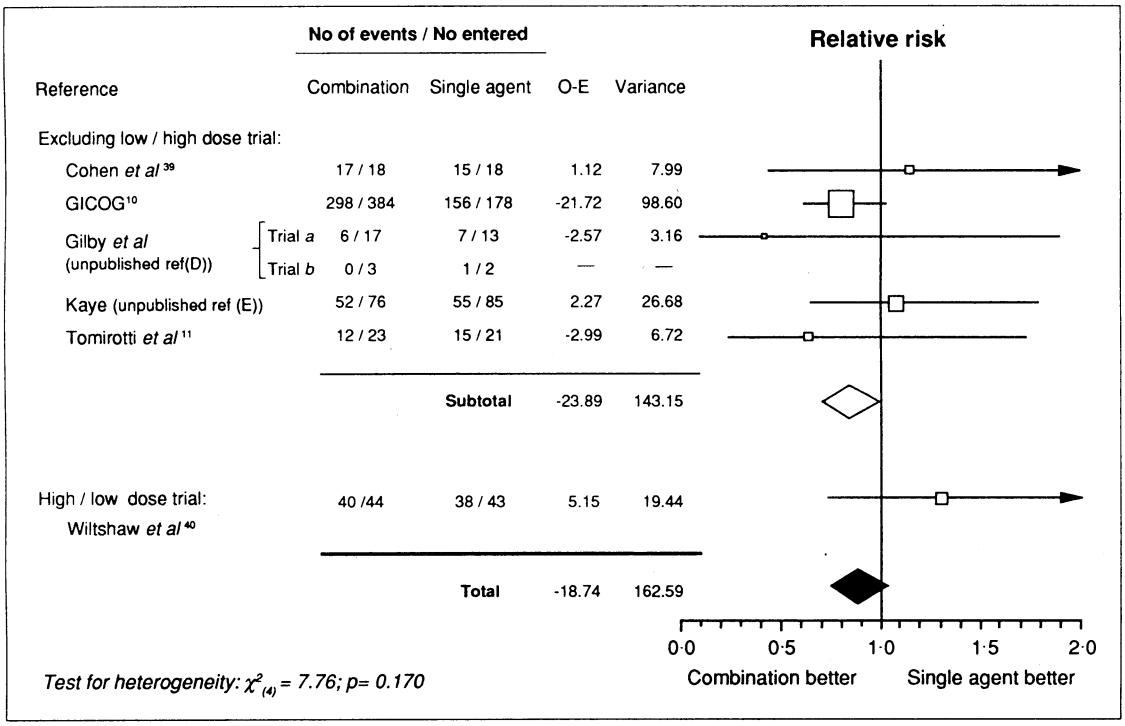

FIG 8—*Relative risks for comparison IV. (Details as in legends to figs 2 and 4 and appendix C)*

tions, which, although not significant, suggests a survival benefit associated with using immediate platinum treatment as opposed to not giving or delaying platinum until relapse.

SURVIVAL PATTERNS

The survival curves for the comparison of single agent platinum with platinum combinations (comparison IV) seemed to favour the combination arm after two years, in contrast with the earlier treatment advantage suggested in comparisons II and III. A possible explanation might be that in comparison IV both treatment groups received some form of immediate platinum treatment. Thus the comparison did not suffer from the problem of "control" patients receiving platinum on relapse from which, arguably, they might derive a late benefit. The results of the analyses imply that platinum in combination is more effective than single agent platinum in the doses used, particularly after two years. Notably, however, in most studies the dose of platinum used as a single agent was lower than is currently used. It will therefore be important to determine whether the apparent difference between treatments was due solely to the addition of other drugs or was, in fact a question of dose as implied in the study by Wiltshaw *et al.*[40] If so, patients receiving drug combinations fared better simply because they received a higher dose of drug irrespective of type.

Similar results and a similar problem of dose were found in a separate overview[60] which examined the role of doxorubicin in ovarian carcinoma. That overview, which reviewed studies of cyclophosphamide, doxorubicin, and cisplatin (CAP) versus cyclophosphamide and cisplatin (CP), found a significant survival advantage for patients treated with CAP over those treated with CP but also concluded that the observed difference might have been due simply to patients in the three drug combination arm having higher total doses of drugs. The only way to resolve this is by comparing currently favoured doses of single agent platinum with platinum combinations in a large prospective randomised clinical trial.

The results of the comparison of cisplatin and carboplatin (comparison V) offer no good evidence that cisplatin is either superior or inferior to carboplatin in terms of survival when given either as a single agent or in combination. Some of the trials included in this comparison, however, were at a comparatively early stage of follow up, so that although the information presented on the first four years was reliable, further follow up was required. It should also be noted that the trials included in comparison V used doses of carboplatin based on surface area rather than on renal clearance as currently recommended.[61]

It is clear from the confidence intervals associated with the overall relative risks that even combining the results from many studies does not provide enough patients to make any firm statements about the results of the comparisons except perhaps for the first one. Comparisons of platinum with non-platinum regimens (comparisons II and III) each contained fewer than

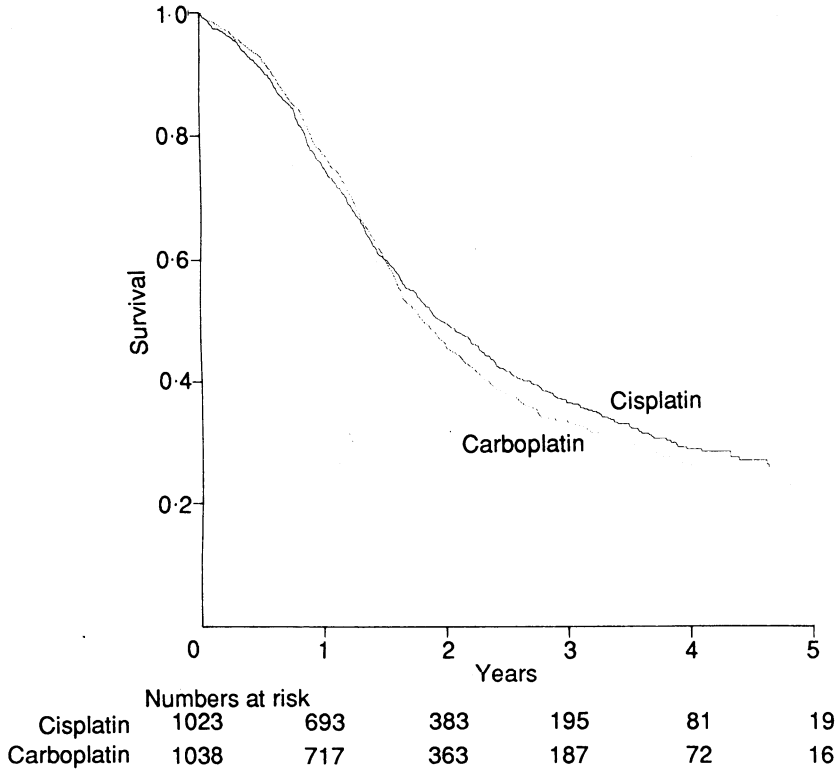

FIG 9—*Survival curves for comparison V (cisplatin v carboplatin)*

1500 patients, and the comparison of platinum as a single agent and in combination had fewer than 1000. Consequently, although all of these comparisons were suggestive of treatment benefit associated with first line platinum based combination chemotherapy, no conclusive evidence emerges. Trials of about double the size of these would be required to establish reliably whether these trends represent actual treatment benefits. The comparison of cisplatin and carboplatin approaches such numbers of patients and provides reliable information on fairly short term survival (up to four years), although, as mentioned above, longer follow up is required. This uncertainty emphasises that in the past clinical trials have been an order of magnitude too small to detect the size of differences which this overview suggests may be realistic for currently available chemotherapy regimens.

IMPLICATIONS

Arguably an overview using a cross section of patient types from many different trials is more likely to reflect the real world than an individual trial and therefore to estimate more accurately the type of treatment effects that are generally achievable. Even so, just as an individual trial cannot provide a prescription for treating any individual patient, neither can an overview. Nevertheless, a well conducted overview provides the least biased and most accurate summary of existing information from clinical trials, from which the clinician can make his or her own decisions about disease management.

Despite not being able to provide any firm conclusions about the most effective forms of treatment for advanced ovarian cancer, this overview raises three important hypotheses—namely, (*a*) platinum combinations are generally better than non-platinum regimens as first line treatment (comparisons II and III); (*b*) platinum combinations are generally better than single agent platinum when platinum is used in the same dose (comparison IV (this is supported by the results from the CAP/CP overview,[60] as if the combination of cyclophosphamide, doxorubicin, and cisplatin is superior to cyclophosphamide plus cisplatin it is likely to be superior to standard dose cisplatin alone)); (*c*) cisplatin and carboplatin are equally effective (comparison V).

At the first meeting of the Advanced Ovarian Cancer Trialists Group, held in June 1990, when the results of these analyses were presented in a preliminary form, consideration of the above hypotheses led to the proposal that it would be appropriate to compare the cyclophosphamide, doxorubicin, cisplatin regimen with optimal dose carboplatin in a large international trial. Such a comparison would have important implications for the management of advanced ovarian cancer. As discussed above, even a moderate improvement in survival could prolong the lives of thousands of women worldwide. A null result would be equally important as the lower toxicity of carboplatin when given as a single agent would almost certainly improve a patient's quality of life. An international trial, icon-2 (International collaborative ovarian neoplasm study), has now been set up to compare cyclophosphamide, doxorubicin, and cisplatin versus optimal dose carboplatin and aims at accruing 2000 patients worldwide. A series of independent parallel trials, each with closely similar protocols, are planned, the data from which will be pooled in a prospective overview. The new study will include centres that participated in this overview, but the trial is open to any clinician who wishes to enter patients either as an individual or as part of a group. At present icon-2 has been launched in the United Kingdom and Italy and is recruiting patients.

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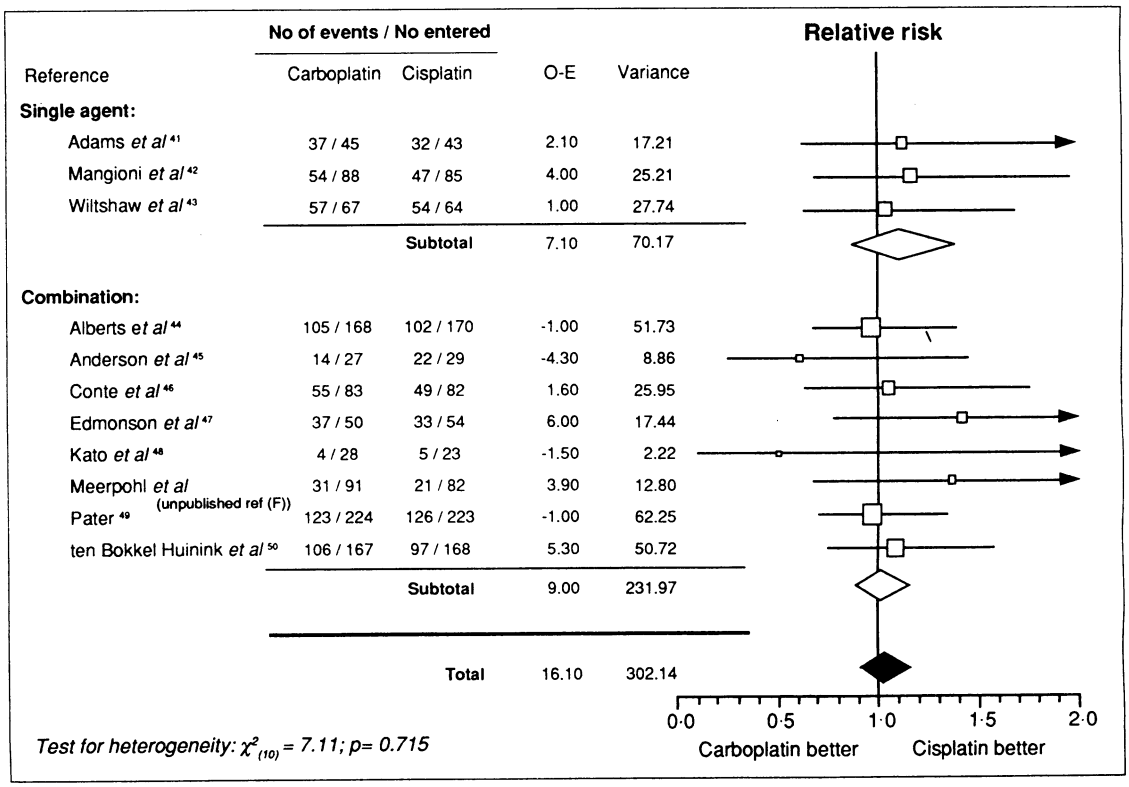

FIG 10—*Relative risks for comparison V. (Details as in legends to figs 2 and 4 and appendix C)*

to all the data centres around the world whose efforts in providing individual patient data made this overview possible.

Organisations and groups that collaborated in the overview were the British MRC, Eastern Cooperative Oncology Group, European Organisation for Research and Treatment of Cancer, German Ovarian Cancer Study Group, Gruppo Intergionale Cooperativo Oncologico Ginecologia, Gruppo Oncologico Nord Ovest, Gynecologic Oncology Group, Gynaecological Group Clinical Oncological Society of Australia, Mario Negri Institute, National Cancer Institute of Canada, Southwest Oncology Group, and the Northern California Oncology Group.

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Appendix A

Details of randomised clinical trials included in advanced ovarian cancer overview

Comparisons I and II

Reference	Single drug	Combination	No of patients in overview
Comparison I: single non-platinum agent v non-platinum combination			
Aabo *et al*[16]	CTX BU	ADR, CTX, FU	179
Bolis *et al*[6]	CTX	ADR, CTX	74
Brodovsky *et al*[17]	L-PAM	CTX, FU, MTX	409
Bruckner *et al*[18]	L-PAM	MTX, TSPA ADR, CTX, FU	331
Chylak *et al*[19]	CTX	ADR, CTX, FU, MTX	69
Edmonson *et al*[20]	CTX	ADR, CTX	111
Miller *et al*[21]	L-PAM	FU, L-PAM, MTX	254
MRC Working Party on Ovarian Cancer[22]	CTX	CTX, HMM, MTX	344
MRC Gynaecological Cancer Working Party (unpublished ref (A))	CTX	ADR, CTX	116
Omura *et al*[23]	L-PAM	ADR, CTX HMM, L-PAM	339
Park *et al*[24]	L-PAM	FU, L-PAM ACT-D, FU, L-PAM ACT-D, CTX, FU	418
Sturgeon *et al*[25]	L-PAM	CTX, FU, HMM, MTX	83
Trope[26]	L-PAM	ADR, L-PAM	168
Turbow *et al*[27]	L-PAM	ADR, CTX	48
Wharton *et al*[28]	L-PAM	CTX. HMM ADR, CTX, HMM	75
Wharton *et al*[28]	L-PAM ADR HMM	CTX, HMM	128
Comparison II: single non-platinum agent v platinum combination			
Bell *et al*[29]	CLB	CTX, CACP	38
COSA[30]	CLB	CLB, CACP	370
Crowther (unpublished ref (B))	CTX	BLE, CTX, CACP	109
Decker *et al*[31]	CTX	CTX, CACP	42
Leonard *et al*[32]	PRED	FU, HMM, PRED, CACP	80
Masding *et al*[33]	TREO	TREO, CACP	157
MRC Gynaecological Cancer Working Party (unpublished ref (A))	CTX	CTX, CACP	100
Sturgeon *et al*[25]	L-PAM	ADR, CTX, CACP	83
Wilbur *et al*[34]	CTX	CTX, CACP	11
Williams *et al*[35]	CLB	ADR, CTX, CACP	89
Vogl *et al*[36]	L-PAM	ADR, CTX, HMM, CACP	250

Comparisons II-V

Reference	Arm 1	Arm 2	No of patients in overview
Comparison III: addition of platinum to regimen			
COSA[30]	CLB	CLB, CACP	370
Decker *et al*[31]	CTX	CTX, CACP	42
De Oliveira *et al*[37]	ADR, CTX	ADR, CTX, CACP	149
Masding *et al*[33]	TREO	TREO, CACP	157
MRC Gynaecological Cancer Working Party (unpublished ref (A))	CTX	CTX, CACP	100
Omura *et al*[23]	ADR, CTX	ADR, CTX, CACP	495
Turbow (unpublished ref (C))	ADR, CTX	ADR, CTX, CACP	84
Wilbur *et al*[34]	CTX	CTX, CACP	11
Comparison IV: single-agent platinum v platinum combination			
Cohen *et al*[39]	CACP	ADR, CACP	36
GICOG[10]	CACP	ADR, CACP ADR, CTX, CACP	562
Gilby *et al* (unpublished ref (D))	CACP	IFOS, CACP	30
	CBDSA	IFOS, CBDSA	5
Kaye (unpublished ref (E))	CBDSA	CLB, CBDSA	161
Tomirotti *et al*[11]	CACP	ADR, CTX, CACP	44
Wiltshaw *et al*[40]	CACP	CLB, CACP	87
Comparison V: cisplatin v carboplatin			
Adams *et al*[41]	CBDSA	CACP	88
Mangioni *et al*[42]	CBDSA	CACP	173
Wiltshaw *et al*[43]	CBDSA	CACP	131
Alberts *et al*[44]	CTX, CBDSA	CTX, CACP	338
Anderson *et al*[45]	CBDSA, CTX	CACP, CTX	56
Conte *et al*[46]	ADR, CTX, CBDSA	ADR, CTX, CACP	165
Edmonson *et al*[47]	CTX, CBDSA	CTX, CACP	104
Kato *et al*[48]	ADR, CTX, CBDSA	ADR, CTX, CACP	51
Meerpohl *et al* (unpublished ref (F))	CTX, CBDSA	CTX, CACP	173
Pater[49]	CTX, CBDSA	CTX, CACP	447
ten Bokkel Huinink *et al*[50]	ADR, CTX, HMM, CBDSA	ADR, CTX, HMM, CACP	335

ACT-D=Actinomycin D. ADR=Doxorubicin. BLE=Bleomycin. BU=Busulphan. CACP=Cisplatin. CBDSA=Carboplatin. CLB=Chlorambucil. CTX=Cyclophosphamide. FU=Fluorouracil. HMM=Hexamethylmelamine. IFOS=Ifosfamide. L-PAM=Melphalan. MTX=Methotrexate. PRED=Prednimustine. TSPA=Thiotepa. TREO=Treosulfan.

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Unpublished trials included in overview

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(C) Turbow MM. Chemotherapy of advanced ovarian cancer: Adriamycin-cyclophosphamide versus platinum-Adriamycin-cyclophosphamide. Northern California Oncology Group protocol 5091, 1980. (Unpublished.)
(D) Gilby E, Pollard W, Barley V, *et al*. Ovarian cancer trial, 1986. South west oncology study. (Unpublished.)
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Appendix B

Trials not included in advanced ovarian cancer overview

Reference	Single drug	Combination	No of patients randomised
Comparison I: single non-platinum agent v non-platinum combination			
Adams *et al*[51]*	L-PAM	ADR, CTX, FU	40
Barlow *et al*[52]†	L-PAM	ACT-D, CTX, FU	108
Carmo-Pereira *et al*[53]†	CTX	CTX, FU, HMM, MTX	57
Delgado *et al*[54]‡	L-PAM	CTX, FU, HMM	27
De Palo *et al*[55]§	ADR	ADR, L-PAM	29
Gronroos *et al*[56]‡	TREO	CTX, TREO ADR, FU, TREO	108
Senn *et al*[57]‖	CTX	CTX, FU	89
Young *et al*[5]§	L-PAM	CTX, FU, HMM, MTX	80
Comparison II: single non-platinum agent v platinum combination			
Carmo-Pereira *et al*[58]†	CTX	CACP, ADR, HMM	59
Harvey *et al*[59]§	L-PAM	CACP, ADR, CTX, HMM	40

*Trial unavailable because data lost.
†Trial unavailable because of inability or unwillingness of those responsible to collaborate in overview.
‡Trial ineligible because did not seem appropriately randomised.
§Trial currently unavailable but promised at later date.
‖Trial unavailable because data destroyed.
ACT-D=Actinomycin D. ADR=Doxorubicin. BLE=Bleomycin.
BU=Busulphan. CACP=Cisplatin. CBDSA=Carboplatin.
CLB=Chlorambucil. CTX=Cyclophosphamide. FU=Fluorouracil.
HMM=Hexamethylmelamine. IFOS=Ifosfamide. L-PAM=Melphalan.
MTX=Methotrexate. PRED=Prednimustine. TSPA=Thiotepa.
TREO=Treosulfan.

Appendix C

GRAPHICAL ANALYSES OF RELATIVE RISKS IN AVAILABLE TRIALS

In the graphical displays of relative risk in the published and unpublished trials (figs 2, 4, 6, 8, 10) the numbers of patients and deaths are given for each arm of the trials together with the observed minus the expected numbers of deaths for the treatment arm. A negative observed minus expected value indicates that the treatment group fared better than the controls whereas a positive observed minus expected value indicates the opposite. The relative risk for each study is plotted as an open square, whose size is directly proportional to the amount of information in that trial. Horizontal lines extend outwards from this to display the 99% confidence interval. The pooled relative risk is shown as an occluded lozenge whose extremities denote the 95% overall confidence interval. Wider confidence intervals—that is, 99% as opposed to the more conventional 95%—are imposed on the individual trials because the problems of their multiplicity increase the

chance of observing a false positive result.[62] Pooled relative risks for subtotals are shown as open lozenges. The vertical line through unity indicates the point where there is no difference between treatments. Trials indicating an advantage for treatment A lie to the left of this line and those showing advantage to treatment B lie to the right. Individual trials indicating a statistically significant result at the p=0·01 level, lie wholly to one side of the line, such that their confidence intervals will not straddle it.

When trials had multiple treatment arms and made more than one comparison of interest the patients from the relevant arms were included in each appropriate comparison, provided that there had been a direct randomisation between the treatment categories used. Thus two trials[25] (unpublished reference (A)) are included in more than one comparison. In trials where more than one arm was of the same treatment category the patients in these arms were grouped together for analysis. For example, in the trial comparing cisplatin versus cisplatin plus cyclophosphamide versus cisplatin, cyclophosphamide, and doxorubicin[10] the patients from the two combination arms were amalgamated and compared with the patients assigned single agent treatment. Two trials stopped randomising to certain arms early,[23,24] and a further two studies employed two separate randomisation schemes[23] (unpublished reference (A)). Each of these trials was subdivided into the appropriate number of data sets, and for analysis each was treated as an independent trial and labelled *a*, *b*, etc.

Risk of fatal coronary heart disease in familial hypercholesterolaemia

Scientific Steering Committee on behalf of the Simon Broome Register Group

Abstract

***Objectives*—(*a*) To determine the excess mortality from all causes and from coronary heart disease in patients with familial hypercholesterolaemia; (*b*) to examine how useful various criteria for selective measurement of cholesterol concentration in cardiovascular screening programmes are in identifying these patients.**

***Design*—Prospective cohort study.**

***Setting*—Eleven hospital outpatient lipid clinics in the United Kingdom.**

***Patients*—282 men and 244 women aged 20-74 with heterozygous familial hypercholesterolaemia.**

***Main outcome measure*—Standardised mortality ratio, all adults in England and Wales being taken as standard (standardised mortality ratio=100 for standard population).**

***Results*—The cohort was followed up for 2234 person years during 1980-9. Fifteen of the 24 deaths were due to coronary heart disease, giving a standardised mortality ratio of 386 (95% confidence interval 210 to 639). The excess mortality from this cause was highest at age 20-39 (standardised mortality ratio 9686; 3670 to 21 800) and decreased significantly with age. The standardised mortality ratio for all causes was 183 (117 to 273) and also was highest at age 20-39 (standardised mortality ratio 902; 329 to 1950). There was no significant difference between men and women. Criteria for measurement of cholesterol concentration in cardiovascular screening programmes (family history, presence of myocardial infarction, angina, stroke, corneal arcus, xanthelasma, obesity, hypertension, diabetes, or any of these) were present in 78% of patients.**

***Conclusions*—Familial hypercholesterolaemia is associated with a substantial excess mortality from coronary heart disease in young adults but may not be associated with a substantial excess mortality in older patients. Criteria for selective measurement of cholesterol concentration in cardiovascular screening programmes identify about three quarters of patients with the clinically overt condition.**

Scientific Steering Committee of the Simon Broome Register Group
Members of the scientific steering committee and participating physicians and clinics are listed at the end of this report.

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Introduction

Familial hypercholesterolaemia is an autosomal dominant disorder of lipoprotein metabolism characterised by mutations of the low density lipoprotein receptor resulting in an accumulation of low density lipoprotein cholesterol in the plasma.[1] Heterozygous familial hypercholesterolaemia has been estimated to affect about one in 500 of the British population.[1] Most affected subjects remain undiagnosed.

It is generally accepted that patients with familial hypercholesterolaemia are at greater risk of coronary heart disease than those with polygenic hypercholesterolaemia. The first report of a substantially increased risk in heterozygous familial hypercholesterolaemia described a 51% chance of fatal or non-fatal coronary heart disease by the age of 50 in men and a corresponding risk of 12% in women.[2] That and most subsequent studies were retrospective analyses, which are subject to inherent biases. Only one study seems to have followed up a large cohort of patients (588 heterozygous familial hypercholesterolaemic patients[3]), and no life table survival analysis has been reported. Published data on morbidity and mortality relate to a time when most patients did not receive effective lipid lowering treatment. A reassessment of the mortality associated with familial hypercholesterolaemia is therefore appropriate as the widespread use of lipid lowering drugs during the past decade, especially bile acid sequestrants and fibric acid derivatives, may have reduced cardiovascular morbidity and mortality.

We have recruited a cohort of patients with definite or possible familial hypercholesterolaemia, which will allow epidemiological, clinical, genetic, and metabolic studies to be performed in a well characterised population. We report the characteristics of 526 patients with definite familial hypercholesterolaemia and their mortality during the first 10 years of follow up. We have also used the information collected at registration to examine how useful the various criteria for selective measurement of cholesterol concentration suggested for use in cardiovascular screening programmes[4] are in identifying such patients.

Patients and methods

Recruitment of patients to the Simon Broome Register of Familial Hyperlipidaemia began in 1980. Patients were registered by the participating lipid clinics, to which they had been referred by either general practitioners or hospital specialists. Three categories of patients were admitted to the register: those defined as having definite familial hypercholesterolaemia, whose families contained at least one member in whom tendon xanthomas were present; those with possible familial hypercholesterolaemia, whose families had no member affected with tendon xanthomas; and a much smaller group with severe hypertriglyceridaemia. We report on patients who were classified as having definite familial hypercholesterolaemia. This was defined as a total cholesterol concentration above 7·5 mmol/l or, when available, a low density lipoprotein cholesterol concentration