Survival Benefits With Diverse Chemotherapy Regimens for Ovarian Cancer: Meta-analysis of Multiple Treatments

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Background: **Numerous randomized trials have compared different chemotherapy regimens in women with ovarian cancer. Although ovarian cancer survival has improved in recent years, the magnitude of these incremental benefits across diverse regimens is unclear.** ***Methods:*** **We used multiple-treatment meta-analysis methodology to combine information from direct and indirect comparisons of all chemotherapy regimens used in randomized trials of ovarian cancer in the last 40 years. Chemotherapy was categorized by the use or not of platinum and/or taxanes, combinations of agents, and intraperitoneal administration. Monte Carlo simulations were used to determine which regimen most improved survival. Analyses of trials that examined first- and second-line treatments were also performed separately.** ***Results:*** **We found 198 trials (N = 38 440 women) involving 120 different chemotherapy regimens published in 1971–2006. Eighty-two trials compared different types of chemotherapy, among which 60 had usable survival information (N = 15 609 women). Monte Carlo simulations showed a 92% probability that the regimen that best prolonged survival is a platinum and taxane combination with intraperitoneal administration; this regimen resulted in a 55% relative risk reduction (95% confidence interval [CI] = 39% to 67%) for mortality as compared with nonintraperitoneal monotherapy using neither platinum nor taxane. Against that same monotherapy comparator, platinum-based combinations with and without intraperitoneal administration achieved 40% (95% CI = 21% to 54%) and 30% (95% CI = 20% to 38%) relative risk reductions for mortality, respectively, and combinations involving platinum and taxane without intraperitoneal administration achieved a 42% (95% CI = 31% to 51%) relative risk reduction. Results were similar when analyses were limited to first-line treatment. Data on second-line treatment were consistent with the superiority of platinum and taxane combinations.** ***Conclusions:*** **Distinct incremental improvements in survival have been achieved for ovarian cancer chemotherapy over time, with the possibility to achieve a doubling or more of time to mortality with platinum and taxane combinations, especially when intraperitoneal administration is used. [J Natl Cancer Inst 2006;98:1655–63]**

Ovarian cancer is a major cause of death worldwide, and it is especially prevalent in developed countries *(1–5)*. The overall 5-year survival rate is poor, at approximately 30% for women older than 65 years *(6)*. Typically, primary treatment consists of surgery and some form of chemotherapy *(7,8)*. Alkylating agents were used initially, with poor results, but platinum-based chemotherapy has improved outcomes in the last 25 years *(9–12)*. In the last 10 years, evidence has also started to accumulate that taxanes and their combination with platinum agents may further improve outcomes *(7,13–17)*. Data from recent studies also suggest that additional benefits are achieved by intraperitoneal chemotherapy *(18)*.

Although there is wide consensus that chemotherapy prolongs survival in women with epithelial ovarian cancer, the exact magnitude of the survival benefits with various regimens is unclear. Approximately, 200 randomized trials comparing different chemotherapy regimens for ovarian cancer have been published. Because newer or more intensive regimens also have higher toxicity, it is important to quantify the incremental survival benefits, if any, conferred by each type of chemotherapy as compared with older regimens.

Here we performed an overview of all randomized trials comparing chemotherapy regimens in patients with ovarian cancer. We aimed to present the evolution of the randomized evidence over time as newer regimens were tested. We examined whether specific regimens are superior to others and evaluated the magnitude of the benefit. Given the wide spectrum of comparisons available, we used multiple-treatment meta-analysis *(19–21)*. This method allowed us to integrate data from both direct and indirect comparisons of diverse regimens.

Methods

Search Strategy and Eligibility Criteria

We searched MEDLINE, EMBASE, and the Central Registry of Controlled Trials of the Cochrane Library (1965 until January 2006). The search strategy used "ovarian cancer or neoplasia" and "chemotherapy" with an array of terms suggestive of randomized trials *(22)*. The full strategy is available on request. We also perused the references of retrieved articles and of previous meta-analyses. Additional cross-searches were performed in MEDLINE using the names of investigators who were the lead authors of at least one eligible trial. In addition, we hand-searched

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several years of the journals with the highest number of electronically identified trials *(23)*.

We considered all randomized controlled trials published in English, German, French, or Italian that compared at least two arms of different chemotherapy regimens (different agents and/or schedules) in at least five patients with ovarian cancer. Trials were included regardless of stage and line of treatment. Trials with at least three arms were included if at least two arms addressed an eligible comparison; noneligible arms were excluded. We excluded meeting abstracts; nonrandomized trials and pseudorandomized trials with alternate allocation of subjects; data on other malignancies or nonepithelial ovarian cancer; trials comparing radiotherapy, immunotherapy, hormonal therapy, and gene therapy (unless the above regimens were the same in all compared arms and the difference between arms pertained to the chemotherapeutic regimens only); and comparisons of chemotherapy against no chemotherapy (best supportive care). In cases of overlap or duplicate reports, we retained only the survival data with the maximal follow-up.

Data Extraction

From each eligible trial, we recorded the first author, publication year, journal, country or countries of the investigators, sample size (randomized and considered eligible for survival analyses [total and per arm]), regimens compared, the line of chemotherapy, previous chemotherapy, stage(s) of the disease, and percentage of patients with performance status 2 or worse (Karnofsky score ≤ 70) per arm.

The type of chemotherapy regimen was categorized according to whether it involved platinum, taxane, both, or neither; used a combination of agents or monotherapy; and used intraperitoneal administration of any agents or not. Theoretically, this categorization gives rise to 14 possible types of chemotherapy, not all of which have necessarily been tested in trials.

For each trial, we recorded the median survival and the number of deaths per arm, if available, and whether there was a statistically significant difference in survival between the compared arms (two-tailed $P<.05$). When several analyses were reported, we preferred the log-rank test results over other statistics and unadjusted analyses over adjusted analyses. For trials including at least two arms, statistical significance was assessed for an analysis considering all arms.

For trials that compared at least two different types of chemotherapy regimens, we also extracted or estimated the hazard ratio (HR) and its variance. We used the reported hazard ratios and 95% confidence intervals (CIs) from Cox regression models. Unadjusted hazard ratios were preferred over multivariable ones. For trials that did not provide this information on hazard ratios and their uncertainty, we imputed these data by using the number of events (E_1, E_2) and patients (T_1, T_2) in each arm and the presented log-rank P value. We estimated the variance by the formula $(T_1 + T_2)^2/[(E_1 + E_2)T_1T_2]$ and then estimated the natural logarithm of the hazard ratio such that it would have the P value denoted by the log-rank test *(24)*. If the log-rank P value was also not available, we estimated the hazard ratio as the inverse of the ratio of the median survival times from the presented Kaplan–Meier curves assuming exponential survival curves and proportional hazards.

Data were extracted independently by two investigators (MK and JPAI). Discrepancies were discussed to reach consensus.

Statistical Analyses

We generated descriptive statistics for trial and study population characteristics across all eligible trials. We described the types of comparisons and how these had evolved over time.

We conducted a series of meta-analyses summarizing the log hazard ratios for each comparison of two different types of treatment applying random effects *(25)*. Between-study heterogeneity was estimated using the I^2 statistic *(26)*.

Multiple-treatment meta-analysis is a method of synthesizing information from a network of trials *(27,28)*. Trials comparing treatments A and B provide direct evidence on the relative effect size θ^D_{AB} (here the log hazard ratio). However, it is possible that indirect information may also be available through a common comparator, e.g., treatment C. Studies comparing A versus B, B versus C, and C versus A form a simple network. Indirect evidence about the effectiveness of A versus B is given by $\theta^I_{AB} = \theta^D_{AC} + \theta^D_{CB}$. The combination of the direct and indirect estimates θ^D_{AB} and θ^I_{AB} into a single effect size can increase precision while randomization is respected *(27,28)*. The combination of direct and indirect evidence for any given treatment comparison can be extended when ranking more than three types of treatments according to their effectiveness: every study contributes evidence about a subset of these treatments.

Multiple-treatment meta-analysis should be used with caution, and the underlying assumptions of the exchangeability of studies across the entire network should be investigated carefully *(19,28,29)*. Exchangeability means that characteristics of the trials would not greatly modify the magnitude of the treatment effects. Exchangeability was tested by examining heterogeneity and incoherence. Joint analysis of treatments can be misleading if the network is substantially incoherent, i.e., if there is disagreement between indirect and direct estimates θ^I_{AB} and θ^D_{AB}.

We performed multiple-treatment meta-analysis with a linear mixed-effects model. Incoherence was taken into account by applying a model that suggests two levels in random effects—one at the level of general comparison being made (e.g., A versus B) and the other at the level of each specific study *(30)*. The comparison-specific effects follow a distribution with zero mean and standard deviation that reflects the incoherence of the network.

One set of multiple-treatment meta-analysis addressed all eligible trials comparing different types of chemotherapy. However, line of treatment may be an important confounder. Therefore, we also considered two separate analyses: one that included only trials that addressed first-line treatment and another that included trials that addressed second-line therapy.

Analyses were conducted in R, version 2.2.1 (R Institute, Vienna, Austria) using lme functions. We also estimated the probability for each type of treatment to be the best at prolonging survival, given the results of the multiple-treatment meta-analysis, using Monte Carlo simulations in WinBUGS, version 1.4 (MRC Biostatistics Unit, Cambridge, U.K., http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml). A major advantage of working within a Bayesian framework is that probabilistic statements about the effectiveness of the different treatments can be made. The prior assumption is that all treatments are equally likely to be the best. For example, the probability of a treatment T_i to be the best out of N treatments can be calculated as the posterior probability $P(\text{Rank}(T_i) = N)$. In WinBUGS code, P.most.effective<-equals(rank(mean[],i),N).

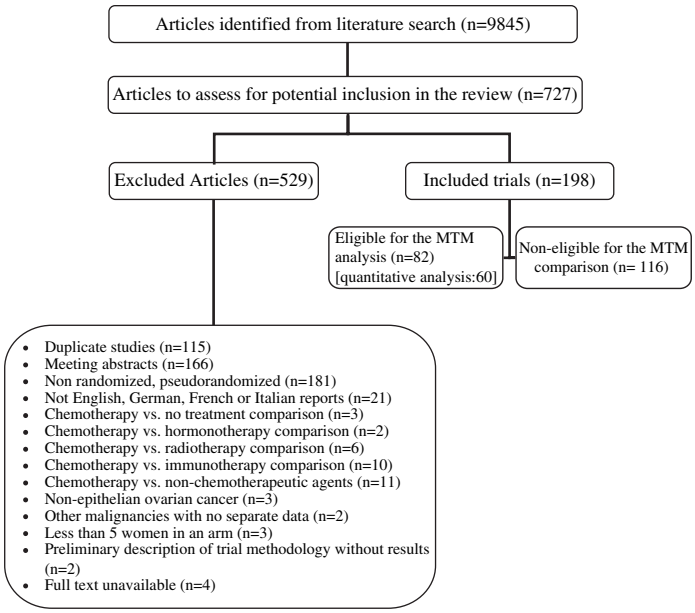

Fig. 1. Flow chart for included and excluded trials. MTM = multiple-treatment meta-analysis.

Results

Eligible Trials

The electronic searches yielded 4653 items from MEDLINE, 3276 from EMBASE, and 1916 from Cochrane Central. Of these, 727 potentially eligible articles were scrutinized. We excluded 529 reports that did not meet eligibility criteria (Fig. 1), leaving 198 trials that qualified for the overview.

The 198 trials (Table 1; Supplementary Data, available at: http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol98/issue22) had been published from 1971 to January 2006. The median sample size was 103 patients (interquartile range = 53–234 patients). Only four trials had more than 1000 subjects; 18 had more than 500 subjects. A total of 38 440 subjects were randomly assigned across 421 arms, and 36 029 subjects were included in survival analyses. In most reports, no previous chemotherapy had been given. There was considerable variability in the percentage of patients with poor performance status, but the percentage of such enrolled patients decreased over time (−6% per decade, $P = .003$). In only two trials did the majority of patients have stage I disease. Most trials were done in the United States and in Europe (Table 1). Only 5% of the studies included one or more intraperitoneally administered agents.

Eighty-two of the 198 trials compared different types of regimens according to our a priori categorization. Overall, this set of 82 trials had a similar profile as the total dataset of 198 trials (Table 1).

Compared Chemotherapy Regimens

A total of 120 different regimens were tested in the 198 trials. Only six monotherapies and 15 combinations of different agents had been tested in at least four trial arms each (Supplementary Table 1, available at: http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol98/issue22). Moreover, doses and schedules of the same regimen often differed across trials. The most commonly used regimen—cisplatin, cyclophosphamide, and doxorubicin—had been used in 34 arms, followed by cisplatin and cyclophosphamide (n = 33 arms), paclitaxel (n = 24), cisplatin (n = 23), carboplatin (n = 21), and carboplatin and paclitaxel (n = 19). Nonplatinum, nontaxane regimens dominated trials published in the 1970s, platinum-based combinations prevailed in the 1980s and 1990s, and combinations including platinum and taxane are the most common regimens used recently (Table 2).

Of 116 trials that compared only regimens of the same type, only six found statistically significant differences in survival (Supplementary Table 2, available at: http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol98/issue22). The percentage (5%) is not beyond what is expected by chance. In two trials with statistically significant differences, the median survival difference between the compared arms was less than 2 months. Three trials showed differences among different regimens involving platinum, but there were 59 trials comparing different platinum-based regimens. One small trial found differences of borderline statistical significance between two regimens involving neither platinum nor taxanes among 29 trials that compared such regimens. Therefore, although minor differences between regimens using the same classes of drugs cannot be totally excluded, these differences would probably be very small overall, if not chance findings.

Table 1. Characteristics of the eligible trials

Characteristic	All randomized trials (N = 198)	Trials comparing different types of treatment (n = 82)
Year of publication		
1971–1980	26	10
1981–1990	61	28
1991–2000	69	30
2001–2006	42	14
Total sample size, median (IQR)*	103 (53–234)	108 (63–240)
Eligible subjects, median (IQR)*	100 (51–223)	104 (57–231)
No. of eligible arms		
Two	178	70
Three	15	8
Four or more	5	4
Previous chemotherapy given, n (%)	48 (24.2)†	15 (18.3)†
Including patients with other malignancies, n (%)	8 (4)	1 (1.2)
Other ineligible trial arms also involved, n (%)	9 (4.5)	3 (3.7)
Performance status ≥2 or Karnofsky ≤70 in more than 50%, n (%)	3 (3.4)‡	1 (2.9)‡
Including >50% with stage I disease, n (%)	2 (1)	0 (0)
Countries involved (investigator affiliations)		
United States	60	26
Multiple countries	44	19
United Kingdom	21	8
Italy	19	11
Germany	8	0
Japan	6	0
Greece	4	3
Austria	4	3
Canada	4	1
Denmark	4	1
The Netherlands	4	1
Other	20	9

*IQR = interquartile range.

†Forty and 14 trials included exclusively patients who had received previous chemotherapy, respectively.

‡Data available for 88 of the 198 and 34 of the 82 trials, respectively.

Table 2. Number of arms per decade that used each regimen (% per decade)*

Regimens	1971–1980	1981–1990	1991–2000	2001–2006
NP/NT monotherapy	36 (60)	25 (19)	8 (6)	14 (16)
NP/NT combination	19 (32)	33 (25)	9 (6)	0
NP/NT monotherapy (ip)	0	0	2 (1)	0
NP/NT combination (ip)	0	1 (1)	0	0
Platinum monotherapy	3 (5)	12 (9)	24 (17)	5 (6)
Platinum-based combination	2 (3)	59 (45)	76 (53)	17 (20)
Platinum monotherapy (ip)	0	0	2 (1)	0
Platinum-based combination (ip)	0	0	4 (3)	1 (1)
Taxane monotherapy	0	0	10 (7)	13 (15)
Taxane-based combination	0	0	1 (1)	1 (1)
Taxane monotherapy (ip)	0	0	0	0
Taxane-based combination (ip)	0	0	0	0
Platinum + taxane–based combination	0	0	8 (6)	34 (39)
Platinum + taxane–based combination (ip)	0	0	0	2 (2)

*NP/NT = nonplatinum and nontaxane agents; ip = including at least one agent given intraperitoneally.

Comparisons of Different Types of Regimens

Of the 82 trials comparing different types of regimens, 60 had survival data (Table 3; Supplementary Table 3 and Supplementary Fig. 1, available at: http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol98/issue22), and these were included in quantitative syntheses (16 478 randomly assigned subjects, 15 609 in survival analyses). The other 22 trials (1380 randomly assigned subjects) were typically phase 1/2 or phase 2 trials with no usable survival data.

We first made pairwise comparisons of regimens from the 60 trials based on direct evidence only (Fig. 2). Heterogeneity ($I^2 > 35\%$) was found only for the comparison of platinum-based combinations versus platinum and taxane–based combinations ($I^2 = 70\%$, four studies), among which three trials using a cisplatin background found a statistically significant survival benefit for the addition of taxane, whereas the trial with a carboplatin background found no such benefit. Direct comparisons showed that platinum monotherapy was statistically significantly better than monotherapy with a nonplatinum, nontaxane agent, and a platinum-based combination was better than monotherapy or combinations involving neither platinum nor taxanes (relative risk reduction of mortality [RRR] = 37%, 22%, and 23%, respectively). Moreover, combinations involving neither platinum nor taxane were better than monotherapy with such agents (RRR = 17%), platinum and taxane–based combinations were better than platinum-based combinations (RRR = 21%), and intraperitoneal administration improved survival with platinum and taxane–based combinations (RRR = 21%).

Multiple-Treatment Meta-analysis

We next performed multiple-treatment meta-analysis of all 60 trials with survival data (Table 4). The combination of nonplatinum and nontaxane agents (not given intraperitoneally) was associated with a small decrease in mortality risk (RRR = 13%) compared with monotherapy with a nonplatinum, nontaxane agent. Platinum monotherapy (RRR = 32%) or platinum-based combination therapy with (RRR = 40%, 95% CI = 21% to 54%) or without (RRR = 30%, 95% CI = 20% to 38%) intraperitoneal administration was associated with more prominent statistically significant survival benefits than nonplatinum agents. Data on taxane-based regimens were sparse, and no formally statistically significant survival benefits were found. Combinations involving both platinum and taxane achieved the most impressive benefits (when intraperitoneal administration was involved, RRR = 55%, 95% CI = 39% to 67%, otherwise RRR = 42%, 95% CI = 31% to 51%).

Monte Carlo simulations showed a 92% probablilty that combinations of platinum and taxane with intraperitoneal administration were the most effective regimens, whereas there was a 6% probability that the best regimen was platinum-based combination chemotherapy with intraperitoneal administration. Therefore, it was 98% likely that the most effective regimen included intraperitoneal administration. The probability that any other type of regimen was the best for prolonging survival was less than 2%. Similar results were seen also in a more simplified multiple-treatment meta-analysis that merged the nonplatinum–nontaxane monotherapy and combination regimens in the same treatment category (Supplementary Table 4, available at: http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol98/issue22).

According to the two-level random-effects model, no important incoherence between comparisons was detected (incoherence = .001). Only one particular comparison loop showed incoherence. Specifically, in the direct comparison, platinum monotherapy was marginally better than taxane monotherapy (HR = 0.87, 95% CI = 0.71 to 1.06), but it was much better based on indirect evidence from the comparison of these two regimens against monotherapy with nonplatinum, nontaxane agents (HR = 0.53, 95% CI = 0.36 to 0.80). The reason for this incoherence was that this comparison loop includes both trials with exclusively first-line treatment and trials with patients on second-line treatment. The nonplatinum, nontaxane regimens for second-line treatment included topotecan, which was not included in first-line therapy. Furthermore, hazard ratios estimated from direct analyses limited to first-line treatments were not materially different from those estimated from analyses of both first- and second-line therapies (Table 4).

Given the small number of trials assessing second-line treatment, the multiple-treatment meta-analysis method is unstable and thus potentially unreliable for the analysis of second-line treatments. There was a suggestion that platinum and taxane–containing combinations could result in a borderline statistically significant relative risk reduction of mortality

Table 3. Trials included with survival data in the multiple-treatment meta-analysis

Author, year	Regimens*	Line	PS (%)	No. (eligible)	No. per arm (eligible)	Median survival (mo)	Stage
ICON, 2002	Pac + CarboPl	I	–	1421 (1421)	478 (478)	36	I–IV
	CarboPl		–		943 (943)	32	
ICON, 2002	Pac + CarboPl	I	–	653 (653)	232 (232)	38	I–IV
	Cyc + Doxo + CisPl		–		421 (421)	40	
Cantu, 2002	Pac	II	–	97 (94)	50 (47)	26	Recurrent
	Cyc + Doxo + cCisPl		–		47 (47)	35	
Bolis, 2001	CarboPl	II	0	190 (190)	95 (95)	24	II–IV/recurrent
	CarboPl + Doxo		0		95 (95)	29	
Yen, 2001	Cyc + Doxo or epirubicin + CisPl (ip)	I	19	132 (118)	− (63)	43	III
	Cyc + Doxo or epirubicin + CisPl (iv)		24		− (55)	48	
Markman, 2001	Pac(iv) + CisPl (iv)	I	11	523 (462)	260 (227)	52	III
	CarboPl (iv) + Pac (iv) + CisPl (ip)		10		263 (235)	63	
Gadducci, 2000	CisPl (ip) + Doxo (iv) + Cyc (iv)	I	2	113 (113)	56 (56)	67	II–IV
	CisPl (iv) + Doxo (iv) + Cyc (iv)		4		57 (57)	51	
Piccart, 2000	Oxaliplatin	II/III	16	86 (81)	45 (42)	42	I–IV/recurrent
	Pac		15		41 (39)	37	
Muggia, 2000	CisPl	I	15	648 (614)	− (200)	30	III–IV
	Pac		14		− (213)	26	
	Pac + CisPl		17		− (201)	27	
Bolis, 1999	Pac	II	–	81 (81)	41 (41)	08	III–IV/recurrent
	Pac + Doxo		–		40 (40)	14	
Parmar/ICON, 1998	CarboPl	I	–	1526 (1526)	760 (760)	33	I–IV
	Cyc + Doxo + CisPl		–		766 (766)	33	
Marth, 1998	CisPl	I	17	181 (176)	− (93)	22	IIb–IV
	CisPl + Cyc		17		− (83)	19	
Athanassiou, 1997	CarboPl	I	–	40 (40)	20 (20)	25†	Ic–IV
	CarboPl + ifosfamide + vincristine + bleomycin		–		20 (20)	14†	
Bolis, 1997	CisPl	I	9	611 (607)	− (301)	31	III–IV
	CisPl + Cyc		11		− (306)	31	
Skarlos, 1996	CarboPl	I	30	130 (130)	73 (73)	28	IIc–IV
	CarboPl + epirubicin + Cyc		30		57 (57)	30	
McGuire, 1996	CisPl + Cyc	I	19	410 (386)	− (202)	24†	III–IV
	CisPl + Pac		17		− (184)	38†	
Trope, 1996	Doxo + melphalan + CisPl	I	–	300 (295)	− (143)	26†	III–IV
	Doxo + melphalan		–		− (153)	18†	
Alberts, 1996	Cyc (iv) + CisPl (ip)	I	15	654 (654)	323 (323)	48†	III
	Cyc (iv) + CisPl (iv)		14		331 (331)	40†	
Wadler, 1996	Melphalan	I	14	253 (244)	123 (118)	18	Recurrent I–II, III–IV, Ic–IV
	Cyc + Hexa + Doxo + CisPl		17		130 (126)	20	
Kirmani, 1994	CisPl (ip) + etoposide (ip) + thiosulfate (iv)	I	21	87 (62)	− (29)	32	IIc–IV
	CisPl (iv) + Cyc (iv)		9		− (33)	36	
Dorum, 1994	CisPl	I	–	171 (171)	85 (85)	20	IIb–IV
	Thiotepa		–		86 (86)	14	
Perren, 1993	Ifosfamide + CarboPl	I	9	152 (135)	− (68)	19	III
	CarboPl		10		− (67)	22	
Krommer, 1992	Cyc + Doxo + CisPl	I	39	83 (83)	41 (41)	24†	III–IV
	Cyc + Doxo + vincristin		48		42 (42)	15†	
Mangioni, 1992	CisPl	I	–	565 (529)	− (173)	19	III–IV
	CisPl + Cyc		–		− (181)	20	
	CisPl + Cyc+Doxo		–		− (175)	23	
Rankin, 1992	CarboPl	I	15	161 (148)	85 (81)	17	IIIvIV
	CarboPl + chlorambucil		18		76 (71)	17	
Sessa, 1991	Hexa + Doxo + Cyc	I	0	120 (110)	57 (53)	23	III–IV
	CisPl + Doxo + Cyc		0		63 (57)	26	
Masding, 1990	Treosulfan	I/II	–	182 (135)	87 (69)	20	IcvIV/recurrent
	Treosulfan + CisPl		–		95 (66)	30	
de Oliveira, 1990	Cyc + Doxo + CisPl	I	28	149 (134)	− (68)	24	III–IV
	Cyc + Doxo		23		− (66)	24	
Leonard, 1989	Hexa + 5-Flu + CisPl + prednimustine	I	15	80 (76)	− (40)	15	III–IV
	Prednimustine		19		− (36)	12	
Trope, 1987	Doxo + melphalan	I	–	168 (148)	− (73)	19†	III–IV
	Melphalan		–		− (75)	11†	
Wilbur, 1987	Cyc	I	–	24 (24)	13 (13)	19	III–IV
	Cyc + CisPl		–		11 (11)	14	
Sevelda, 1987	Doxo + Cyc	I	–	13 (13)	8 (8)	24	Ic, IIc
	Doxo + CisPl		–		5 (5)	>36	
Wiltshaw, 1986	CisPl	I	–	91 (91)	46 (46)	16	III
	CisPl + chlorambucil		–		45 (45)	14	

(Table continues)

Table 3 (continued).

Author, year	Regimens*	Line	PS (%)	No. (eligible)	No. per arm (eligible)	Median survival (mo)	Stage
Williams, 1985	CisPl + Doxo + Cyc	I	–	89 (85)	– (42)	13	III–IV
	Chlorambucil		–		– (43)	11	
Lambert, 1985	CisPl	I	–	86 (86)	49 (49)	19†	III–IV
	Cyc		–		37 (37)	12†	
Barlow, 1985	Melphalan	I	–	108 (96)	54 (49)	12	III–IV
	Actinomycin D + 5-Flu + Cyc		–		54 (47)	13	
Bruckner, 1985	Melphalan	I	18	339 (318)	88 (83)	12	Recurrent I–II, III–IV
	Trie + Meth cross over to Cyc + Doxo + 5-Flu (sequential)		33		80 (73)	12	
	Cyc + Doxo + 5-Flu cross over to Trie + Meth (sequential)		24		86 (82)	14	
	Trie + Meth alternate with Cyc + Doxo + 5-Flu (fixed rotation)		21		85 (80)	15	
Aabo, 1985	dihydroxybusulfan or Cyc	I	–	179 (156)	82 (68)	12	IIb–IV
	Cyc + Doxo + 5-Flu		–		97 (88)	14	
Delgado, 1985	Cyc + Hexa + 5-Flu	I	–	27 (27)	13 (13)	13	Ic, IIc, III–IV
	Melphalan		–		14 (14)	10	
Gronroos, 1984	5-Flu + dactinomycin + vincristine	I	–	108 (108)	30 (30)	06	IV
	Treosulfan		–		41 (41)	09	
	Cyc + 5-Flu		–		37 (37)	10	
Edwards, 1983	Melphalan + CisPl	I	–	169 (158)	– (84)	30	III–IV
	Hexa + Doxo + Cyc		–		– (74)	26	
Adams, 1982	Melphalan	I	–	40 (38)	– (19)	06	III–IV
	Doxo + 5-Flu + Cyc		–		– (19)	08	
Decker, 1982	Cyc	I	–	42 (42)	21 (21)	17†	III–V
	Cyc + CisPl		–		21 (21)	40†	
Carmo-Pereira, 1981	Hexa + Cyc + Meth + 5-Flu	I	–	64 (57)	32 (28)	10	III–IV
	Cyc		–		32 (29)	11	
Scott, 1981	Cyc (oral)	I	–	296 (261)	146 (131)	10	Recurrent
	Cyc + Hexa + Meth		–		150 (130)	12	
Park, 1980	Melphalan	I	–	427 (314)	135 (102)	09	IV/recurrent III–IV
	Melphalan + 5-Flu		–		106 (80)	14	
	Melphalan + 5-Flu + dactinomycin		–		119 (83)	13	
	Cyc + 5-Flu + dactinomycin		–		67 (49)	08	
Neijt, 1991	Hexa + Cyc + Meth + 5-Flu	I	–	196 (186)	– (94)	18†	III–IV
	Cyc + Hexa alternating with Doxo + CisPl		–		– (92)	26†	
Sevelda, 1992	Doxo-CisPl + vincristine-Cyc + Meth (sequentially alternating)	I	–	86 (80)	45 (43)	17	III–IV
	Doxo + Cyc		–		41 (37)	11	
Sevelda, 1992	Doxo + Cyc	I	–	78 (74)	40 (36)	13	III–IV
	Doxo + CisPl		–		38 (38)	16	
Omura, 1991	Melphalan	I	–	432 (319)	110 (84)	12	III, IV, recurrent
	Melphalan + Hexa		–		175 (131)	12	
	Cyc + Doxo		–		147 (104)	14	
Omura, 1991	Cyc + Doxo	I	15	516 (407)	251 (209)	16	III–IV/recurrent III–IV
	Cyc + Doxo + CisPl		18		265 (198)	20	
Young, 1978	Hexa + Cyc + Meth + 5-Flu	I	–	80 (80)	41 (41)	29	III–IV
	Melphalan		–		39 (39)	17	
Pfisterer, 2005	Gemcitabine + CarboPl	II	52	356 (356)	178 (178)	18	Recurrent Ia–IV
	CarboPl		47		178 (178)	17	
Piccart, 2003	CisPl + Pac	I	13	680 (680)	342 (342)	36†	IIb–IV
	CisPl + Cyc		12		338 (338)	26†	
ten Bokkel Huinink, 2004	Topotecan	II	18	235 (226)	117 (112)	15	III–IV/Recurrent
	Pac		17		118 (114)	12	
Kaye, 2005	Pac + platinum-based chemotherapy	II–IV	6	802 (802)	392 (392)	26†	Recurrent
	Platinum-based chemotherapy		6		410 (410)	24†	
Buda, 2004	Pac	II	7	234 (212)	114 (106)	14	Recurrent
	Pac + epirubicin		9		120 (106)	12	
Armstrong, 2006	Pac (iv) + CisPl (iv)	I	4	429 (415)	215 (210)	50†	III
	Pac (iv) + CisPl (ip) + Pac (ip)		7		214 (205)	66†	
Reed, 2005	CarboPl	I	44	204 (204)	102 (102)	15†	Ic–IV
	Treosulfan		46		102 (102)	12†	
Gonzalez-Martin, 2005	CarboPl	II/III	18	81 (78)	40 (40)	17†	Recurrent
	Pac + CarboPl		6		41 (38)	>38†	

*PS = Performance status poor (i.e., 2) or worse; Doxo = doxorubicin; CarboPl = carboplatin; CisPl = cisplatin; Cyc = cyclophosphamide; Pac = paclitaxel; Hexa = hexamethylmelamine; 5-Flu = 5-fluorouracil; Trie = triethylnethiophosphoramide; Meth = methotrexate; – = missing values.

†Statistically significant survival difference. For the meta-analysis calculations, the natural logarithm of the hazard ratio and its variance were derived from the number of events per patients per arm and the log-rank value (as shown in the Methods) for the studies by Marth, Athanassiou, Skarlos, Dorum, Lambert, Krommer, de Oliveira, Leonard, Williams, Gadducci, Kirmani, Bolis, Masding, Aabo, Adams, Decker, Sessa, and Trope 1987.

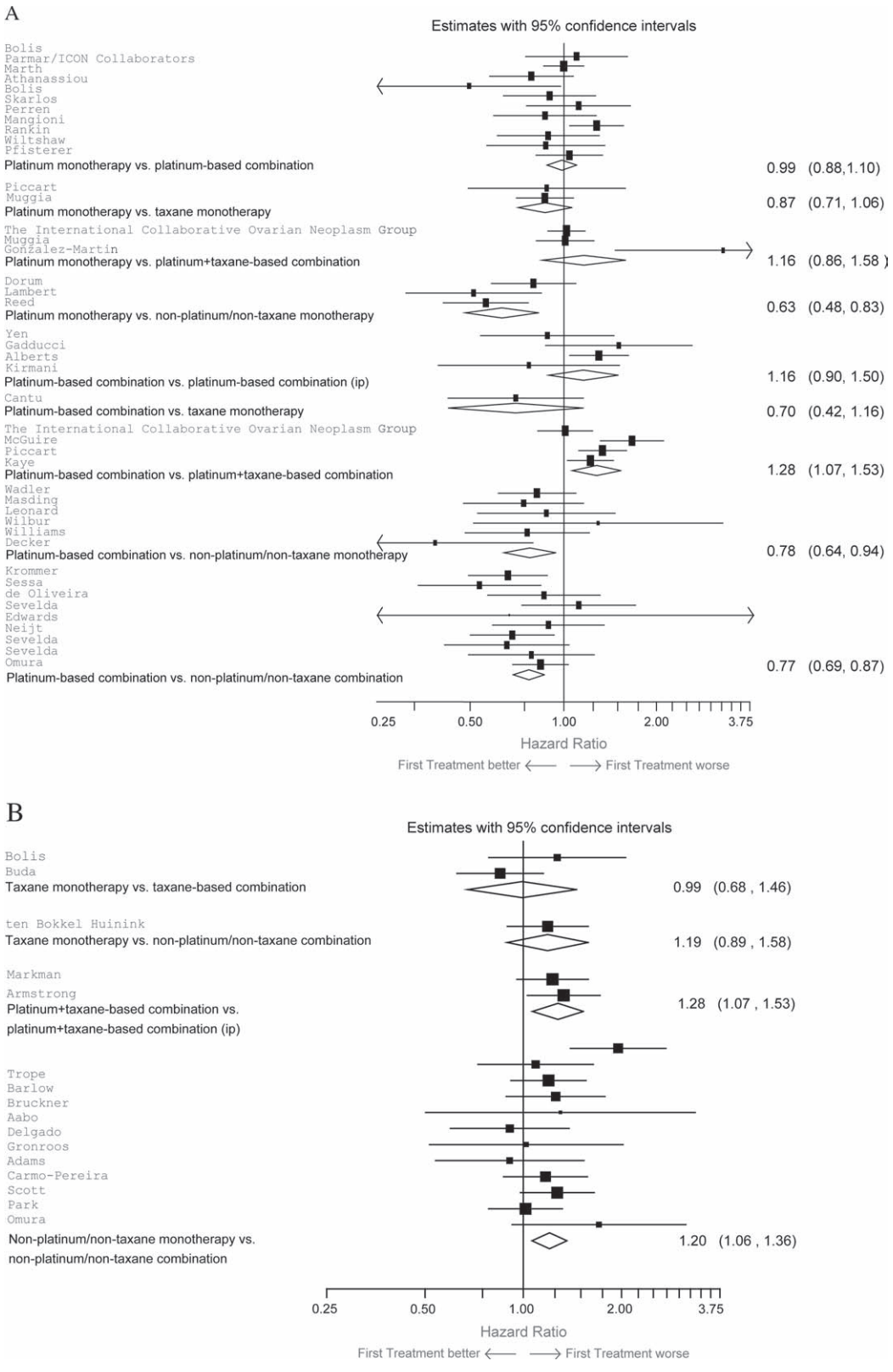

Fig. 2. Hazard ratios (and 95% confidence intervals) for survival in meta-analyses of direct comparisons between various types of chemotherapy. Summary estimates are shown by **diamonds**. Size of symbols is proportional to the inverse variance of the estimate. **A**) Comparisons addressing at least one regimen involving platinum. **B**) Other comparisons. The names of the first author for each study are shown on the **left side**.

against platinum monotherapy (HR = 0.53, 95% CI = 0.29 to 0.96) and taxane monotherapy (HR = 0.47, 95% CI = 0.22 to 0.99). On direct comparison, the hazard ratio for mortality of platinum and taxane–containing combinations versus platinum monotherapy was 0.82 (95% CI = 0.69 to 0.97), while there was no direct comparison of the combination versus taxane monotherapy.

Discussion

We examined 198 randomized trials that compared various chemotherapy regimens in women with ovarian cancer during the last 40 years. We show conclusively the major progress that has been achieved in prolonging the survival of these patients and we have quantified the magnitude of the survival benefit.

Table 4. Multiple-treatment meta-analysis showing hazard ratios (with 95% confidence intervals) for death for each type of regimen as compared with monotherapy that involves neither platinum nor taxane (not ip)*

Regimen	All data, 60 trials	First line only, 51 trials
Platinum monotherapy	0.68 (0.59 to 0.78)	0.64 (0.54 to 0.75)
Platinum-based combination	0.70 (0.62 to 0.80)	0.69 (0.60 to 0.80)
Platinum-based combination (ip)	0.60 (0.46 to 0.79)	0.59 (0.45 to 0.79)
Taxane monotherapy	0.92 (0.74 to 1.16)	0.73 (0.51 to 1.05)
Taxane-based combination	0.95 (0.64 to 1.40)	ND
Platinum + taxane–based combination	0.58 (0.49 to 0.69)	0.57 (0.47 to 0.70)
Platinum + taxane–based combination (ip)	0.45 (0.33 to 0.61)	0.45 (0.32 to 0.62)
NP/NT combination	0.87 (0.78 to 0.97)	0.86 (0.76 to 0.98)

*For both analyses, the common heterogeneity estimate for the log hazard ratios is 0.12. NP/NT = nonplatinum and nontaxane agents; ip = including at least one agent given intraperitoneally; ND = no data.

Compared with the early days, when neither platinum nor taxanes were available and chemotherapy was clearly no better than supportive care for mortality outcomes *(10)*, median survival can now be more than doubled using currently available regimens. A platinum and taxane–based combination with intraperitoneal administration *(18)* can reduce the risk of death by 55%. More than half (30%) of this benefit may be achieved with a standard platinum-based combination. Taxanes without platinum do not appear to confer any clear survival benefit. Although the data pertain predominantly to first-line treatment, the sparse data on second-line treatment are consistent with a superiority of combined platinum and taxane regimens.

The absolute magnitude of the increase in survival time is impressive. For an expected median survival of 2.5 years without effective treatment, approximately 3 years are gained with the most effective current treatments. However, these benefits should be tailored to the individual patient and balanced against tolerability. Multidrug combinations including both platinum and taxanes can cause cumulative toxicities *(14,31,32)*. Intraperitoneal administration in particular has not been used in many centers around the world, and its implementation may cause some challenges *(33)* and extra toxicities *(18)*. Platinum and taxane–based combinations with intraperitoneal administration are the best regimens for survival in our multiple-treatment meta-analysis with very high probability; we estimate that some kind of intraperitoneal regimen is 98% likely to be the best. However, if intraperitoneal administration proves difficult to implement, survival can still be almost doubled with a combination of platinum and taxanes without intraperitoneal administration.

The long-term evolution of cancer chemotherapy therapeutics creates difficulty in estimating the relative merits of regimens that are introduced over a long period of successive steps. Newer regimens are unavoidably compared with previous regimens, rather than to very old agents or no treatment. The multiple-treatment meta-analysis approach is attractive in this setting because it can accommodate such successive steps through loops of indirect comparisons. Multiple-treatment meta-analysis can prove a particularly useful approach to synthesize evidence on medical domains among which data on many treatments accumulate, a scenario that is becoming relatively common in clinical therapeutics *(20)*. However, caution should be used for trials that are distant in time because of the potential danger of confounding with other factors that vary over time, such as supportive or adjunct treatment practices *(34)*.

We should also caution that a full evaluation of the possibility of incoherence for nine treatments would require up to 112 loops to be evaluated in the multiple-treatment meta-analysis framework. In our network, there were many treatment comparisons for which no direct evidence was available and the evaluation of incoherence was impossible. Therefore, some conservative interpretation is warranted, especially for treatments that have been involved in few trials. In this regard, more evidence on regimens that include intraperitoneally administered agents, as well as longer term follow-up of the existing trials, would be useful.

Another possible limitation is that the current analysis is based on published group data, rather than individual-level information. Therefore, we have included women across a wide range of prognoses, from stage I to advanced disease. However, the vast majority of trials did not include any meaningful proportion of data for very early stage disease, a reflection of the fact that most women with ovarian cancer are still diagnosed at relatively advanced stages. Individual-level information might allow a more detailed appraisal of outcomes at different levels of risk *(35)*. Individual-level data would also be useful to address whether there is any effect modification by the type of surgical intervention, stage, and whether residual tumor is left after surgery. In addition to depending on chemotherapy, optimization of outcomes may depend also on the surgical approach. However, the power to detect effect modifications might still be limited, even with individual-level information, in such a complex network of multiple treatments.

It is also notable that, even though almost 40 000 women have participated in published randomized trials of chemotherapy regimens in ovarian cancer, the large majority of investigations pertain to comparisons of similar types of treatment with minor modifications in the dosing or schedule or minor differences in the compared drugs that belong to the same class of agents. Although such trials may still help to improve our understanding of minor variants of different regimens, especially regarding toxicity and tolerability, they are unlikely to result in major progress regarding improvement of survival. The few exceptions of statistically significant survival differences that we have seen in such trials may be real but may also simply reflect chance findings. With many investigators working in this field, it would be useful to design future trials that will fill in important gaps where major loops of evidence have minimal or no information. An efficient strategic plan for clinical research in the field would require infrastructure support. Moreover, there is a need for clinical trials cooperative groups to develop complementary trials, to decrease duplication, and when appropriate, to also perform joint trials. The multiple-treatment meta-analysis can offer an additional impetus to such an effort, and it may also be useful as new regimens, including molecularly targeted treatments *(36,37)*, are developed.

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NOTES

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