Third-Generation Chemotherapy Agents in the Treatment of Advanced Non-small Cell Lung Cancer: A Meta-Analysis

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Purpose: To estimate the efficacy of third-generation (3G) chemotherapy agents (paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan) on response and survival in stage IIIB/IV non-small cell lung cancer (NSCLC).

Methods: A meta-analysis was performed using trials identified through MEDLINE. Results on tumor response and survival were collected from randomized trials comparing 3G monotherapy versus best supportive care (BSC), 3G monotherapy versus second-generation (2G) platinum-based regimens, and 3G platinum-based regimens versus 2G platinum-based regimens.

Results: Of the 2480 citations screened, 20 randomized controlled trials fulfilled the inclusion and exclusion criteria, and 19 trials were used in the analyses. The data from two, three-arm trials were used in two different comparisons. Five trials (n = 1029 patients) compared 3G monotherapy with BSC. The summary risk difference (RD) for 1-year survival favored 3G agents by 7% (95% confidence interval [CI]: 2%, 12%). Four trials (n = 871 patients) compared treatment with 3G monotherapy versus 2G platinum-based regimens. The response RD was −6% (95% CI: −11%, 0%), and the 1-year survival rate RD was 3% (95% CI: −3%, 10%), suggesting that despite a slightly higher response rate for 2G platinum-based regimens relative to 3G monotherapy, there is equivalency in survival. Twelve trials (n = 3995) compared 3G versus 2G platinum-based regimens. The RD for response was 12% (95% CI: 10%, 15%). A RD for 1-year was not calculated, because of heterogeneity among the trials. A subset analysis of 3G versus 2G platinum-based doublets revealed a 1-year survival-rate RD of 6% (95% CI: 2%, 10%), favoring 3G platinum-based regimens without evidence of heterogeneity.

Conclusions: 3G agents have been a significant advance in the treatment of NSCLC.

Key Words: Paclitaxel, Docetaxel, Gemcitabine, Vinorelbine, Irinotecan.

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Lung cancer remains the leading cause of cancer-related mortality among men and women, and in 2007 in the United States more patients will die of lung cancer than of breast, colon, and prostate cancers combined.[1] It is estimated that in the United States in 2007, there will be approximately 213,000 new diagnoses of lung cancer, and 160,000 deaths resulting from lung cancer.[1] Approximately 85% of these cases were non-small cell lung cancer (NSCLC), and two thirds of these patients were stage IIIB or IV at the time of diagnosis.[2–4] For patients with preserved functional status, the current standard of care is double-agent platinum-based chemotherapy.[5] The median survival and 1-year survival rates with platinum-based therapy are 8 to 10 months and 30% to 35%, respectively.[6]

During the 1990s, new agents including paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan emerged as active single agents in stage IIIB/IV NSCLC. These agents have been termed third-generation (3G) agents and have single-agent response rates of 10% to 20%.[7–12] The 3G agents were rapidly adopted in the treatment in advanced NSCLC, although questions remain about their efficacy relative to the previous standard therapies, often referred to as 2G agents or regimens. These regimens include cisplatin alone or in combination with older agents such as etoposide, vindesine, mitomycin, or ifosfamide. Numerous trials have evaluated 3G agents alone or in combination with other agents. Nevertheless, disparate trial designs and comparator arms have been employed, and many trials have not been adequately powered to determine the superiority of one treatment over others.

To determine whether there is an increase in efficacy of the 3G agents, as measured by response and 1-year survival rate, we performed a meta-analysis of randomized trials. A meta-analysis may provide sufficient power to detect statistically and clinically relevant differences in the efficacy of 3G

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agents in comparison with previous therapies. Meta-analyses can be performed using data extracted from the published literature or individual patient data. The use of individual patient data is less likely to overestimate the treatment effect and is more valuable when times to event outcomes are being evaluated.[13] The availability of individual patient data facilitates investigations into the relationships between patient characteristics and treatment and impact on heterogeneity. The use of a definitive endpoint, such as 1-year survival rate, reduces the variability in reporting of the efficacy parameter and the dependency on individual patient data. In addition to detecting clinically relevant differences between treatments, we attempted to quantify the difference between the two treatments. The risk difference (RD) and the number needed to treat (NNT) were calculated to estimate the benefit of treatment with 3G agents.

METHODS

Literature Search

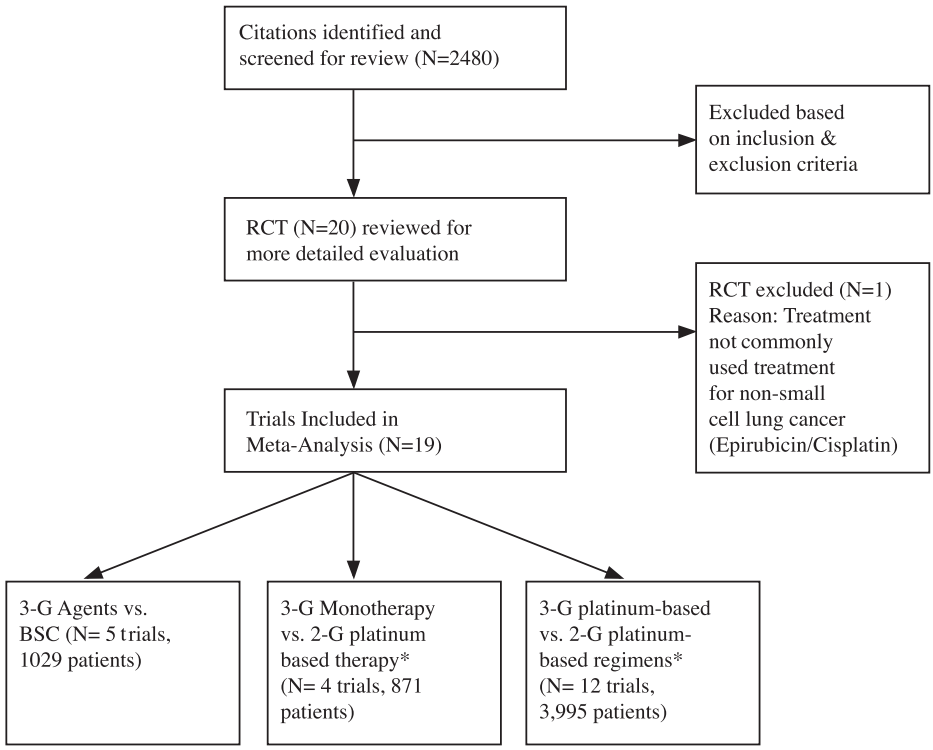
Potentially eligible studies were identified using a MEDLINE search for the period of January 1980 to March 2004. Search terms included the following combined subject headings: paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, lung neoplasms, randomization, and clinical trial. The bibliographies of retrieved randomized clinical trials, meta-analyses, and narrative review articles were reviewed by the authors. The pharmaceutical companies were contacted to identify additional clinical trials involving their 3G agents in NSCLC. The results of these searches were combined to yield a common set of citations from which the titles and abstracts were screened for potential qualifying studies. A citation identified by any of the search strategies was reviewed by all of the investigators. The decision to select an article was based on information available in the published report and was reached by consensus among the study authors.

Inclusion Criteria

3G agents were defined as paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan. 2G regimens were defined as a platinum alone or platinum in combination with older agents including etoposide, vindesine, ifosfamide, and mitomycin. Studies were included only if they were randomized controlled trials published in peer-reviewed journals between January 1980 and March 2004. All patients must have been previously untreated and diagnosed with advanced stage NSCLC. Treatment comparisons could be any one of the following combinations: 3G monotherapy versus best supportive care; 3G monotherapy versus 2G platinum-based regimen; and 3G platinum-based versus 2G platinum-based regimen. Abstracts were not included, because of issues with incompleteness of the data and potential issues with the quality of data abstracted from non–peer-reviewed sources.

Data Abstraction

The following data were abstracted directly from the published trials: type and dosage of chemotherapy, number of patients randomized to each arm of chemotherapy, gender, age, race, performance status, stage, pathologic type, weight



Abbreviations: 3-G = Third Generation; 2-G=Second Generation; RCT = Randomized Controlled Trials
* The relevant data from two 3-arm trials was extracted and used in the comparison of 3G monotherapy vs. 2-G platinum-based therapy, and 3-G platinum-based vs. 2-G platinum-based regimens

FIGURE 1. Selection of trials.

loss >5%, previous radiotherapy, schedule of systemic chemotherapy, response (overall, complete, partial, stable disease, progression), and 1-year survival rate.

Data Analysis

Publication bias was assessed using funnel plots for asymmetry and using the symmetry tests of Begg and Mazumdar,[14] and Sterne et al.[15] These tests examine the association between estimated treatment effects and the precision of the estimates. The Begg and Mazumdar test uses an adjusted rank correlation method, whereas the Sterne et al. test uses a linear regression model. In addition, each group of studies was examined for overall heterogeneity to ensure that synthesis was warranted. The homogeneity p value was required to be >0.1 for a summary RD to be presented. These estimates were computed as inverse-variance weighted aver-

TABLE 1. Characteristics of Studies Included in the Meta-analysis, and Their Patient Populations

First Author or Study Group	Phase	Therapy	Therapy Class	Number of Patients	Median Age (yr)	Percent Male	Percent PS 0–1 KPS > 70%	Percent Stage IIIB	Percent Stage IV
Le Chevalier[16]	III	Cisplatin, vinorelbine	3G platinum based	206	59	88	80	28	50
		Vinorelbine	3G monotherapy	206	60	87	77	32	47
		Cisplatin, vindesine	2G platinum based	200	59	90	82	25	55
Crawford[7]	—	Vinorelbine	3G monotherapy	143	61	71	100	0	100
		5FU/LCV	BSC	68	61	71	100	0	100
Baldini[20]	—	Carboplatin, vinorelbine	3G platinum based	43	61	88	88	33	67
		Cisplatin, ifosfamide, vinorelbine	3G platinum based	48	64	88	87	38	63
		Cisplatin, vindesine, mitomycin	2G platinum based	49	62	84	79	31	69
Giaccone[21]	II/III	Cisplatin, paclitaxel	3G platinum based	155	59	71	87	37	63
		Cisplatin, teniposide	2G platinum based	162	59	70	92	40	60
Wozniak[22]	III	Cisplatin, vinorelbine	3G platinum based	206	63	68	100	8	92
		Cisplatin	2G platinum based	209	63	67	100	8	92
Cardenal[23]	—	Cisplatin, gemcitabine	3G platinum based	69	59	93	83	48	52
		Cisplatin, etoposide	2G platinum based	66	58	92	88	52	49
Crino[24]	III	Cisplatin, gemcitabine	3G platinum based	155	62	85	93	21	79
		Cisplatin, mitomycin, ifosfamide	2G platinum based	152	60	84	95	21	79
ELVIS[8]	—	Vinorelbine	3G monotherapy	76	74	86	76	27	73
		BSC	BSC	78	74	89	76	28	72
ten Bokkel Huinink[17]	II	Gemcitabine	3G monotherapy	72	59	74	82	18	76
		Cisplatin, etoposide	2G platinum based	75	59	81	91	17	75
Perng[18]	II	Gemcitabine	3G monotherapy	27	63	67	89	30	67
		Cisplatin, etoposide	2G platinum based	26	60	62	69	15	81
Anderson[9]	—	Gemcitabine	3G monotherapy	150	65	66	30	59	41
		BSC	BSC	150	64	61	27	61	39
Bonomi[25]	III	Cisplatin, high dose paclitaxel	3G platinum based	201	61	63	100	20	80
		Cisplatin, low-dose paclitaxel	3G platinum based	198	63	62	100	23	77
		Cisplatin, etoposide	2G platinum based	200	62	66	100	15	85
Gatzemeier[26]	III	Cisplatin, paclitaxel	3G platinum based	207	60	80	82	30	70
		Cisplatin	2G platinum based	207	60	81	81	30	70
Ranson[10]	III	Paclitaxel	3G monotherapy	79	65	73	84	49	51
		BSC	BSC	78	64	76	82	41	59
Roszkowski[11]	III	Docetaxel	3G monotherapy	137	59	80	81	56	44
		BSC	BSC	70	60	84	77	47	53
Sandler[27]	III	Cisplatin, gemcitabine	3G platinum based	260	62	70	80	26	67
		Cisplatin	2G platinum based	262	63	71	88	23	70
Gebbia[28]	III	Cisplatin, vinorelbine	3G platinum based	122	61	72	76	55	45
		Cisplatin, vindesine, mitomycin	2G platinum based	125	60	78	71	54	46
Negoro[19]	III	Cisplatin, irinotecan	3G platinum based	129	64	76	94	38	62
		Irinotecan	3G monotherapy	129	62	74	94	34	66
		Cisplatin, vindesine	2G platinum based	122	64	80	94	38	62
Kubota[29]	III	Cisplatin, docetaxel	3G platinum based	151	63	64	96	0	100
		Cisplatin, vindesine	2G platinum based	151	64	68	97	0	100

BSC, best supportive care; 2G, second generation; 3G, third generation.

TABLE 2. Third-Generation Single Agents Compared with Best Supportive Care

First Author or Study Group	Therapy	Number of Patients	Patients Assessable	Overall Response Rate (%)	Survival	
					No. of Patients	1-yr Survival (%)
Crawford[7]	Vinorelbine	143	126	12	143	25
	5FU/LCV	68	58	3	68	16
ELVIS[8]	Vinorelbine	76	70	20	76	32
	BSC	78	—	—	78	14
Anderson[9]	Gemcitabine	150	135	17	150	25
	BSC	150	—	—	150	22
Ranson[10]	Paclitaxel	79	76	16	79	24
	BSC	78	—	—	78	23
Roszkowski[11]	Docetaxel	137	92	20	137	25
	BSC	70	—	—	70	16

BSC, best supportive care.

ages of the estimates from the individual studies. When there was little evidence of heterogeneity or publication bias, summary estimates of the RD were presented. The RD (or absolute risk reduction) is the actual difference in survival rates between two comparison groups and is defined as $\pi_1 - \pi_2$, where π_1 and π_2 are the proportions of patients in study arms 1 and 2 that experience the endpoints of interest, respectively. The NNT is defined as $1/(\pi_1 - \pi_2)$ and represents the estimated number of patients that would need to be treated on the more beneficial study arm to prevent one adverse outcome. Survival at 1 year was based on intent to treat, and response rates were based on the patients who were assessable. Therefore, the number of patients in a survival analysis may exceed the number in a response analysis. All analyses were performed using the STATA statistical software, release 7.0 (Stata Corp, College Station, TX).

RESULTS

Search of the Published Literature

Two thousand four hundred eighty citations were reviewed, and 20 clinical trials met the criteria set forth in the methods section (Figure 1). Examination of review articles, meta-analyses, and retrieved trials did not identify any additional randomized clinical trials appropriate for inclusion in this analysis. One study was rejected because it compared a 3G agent against a 2G platinum-based regimen (epirubicin/cisplatin) that is not commonly used for NSCLC.

Characteristics of Included Studies

A total of 19 studies with 5895 patients were included in this meta-analysis (Table 1).The trials were divided into three groups: (1) all randomized trials that compared 3G agents as single agents to BSC (five trials, $n = 1029$ patients), (2) all randomized trials that evaluated 3G agents as monotherapy compared with 2G platinum-based combination regimens (four trials, $n = 871$ patients), and (3) all randomized trials that compared 3G agents in combination with platinum-based therapy compared with 2G regimens (12 trials, $n = 3995$ patients). All of the trials comparing 3G agents in combination with platinum therapy against 2G regimens were published in or after 1994.

Treatment Comparisons

Five trials ($n = 1029$ patients) compared 3G single agents with BSC (Table 2).[7–11] Four of the trials included a BSC control arm, and one trial included 5-fluorouracil (5FU)/leucovorin as the control arm. This trial was included because the 5-FU/leucovorin control arm had an overall response rate of 3% and a survival profile similar to the BSC arms of the other four trials. Response comparisons were not appropriate for 3G single agents against BSC. Nevertheless, response rates for the 3G agents ranged from 12% to 20%. Comparisons of 1-year survival rates demonstrated little evidence of heterogeneity or publication bias (Table 3). One-year survival favored the 3G agents over BSC (Figure 2), with a summary RD of 7% (95% confidence interval [CI]: 2% to 12%), The NNT for one patient to realize a benefit in the probability of 1-year survival was 14.

Four trials ($n = 871$ patients) compared 3G monotherapy with 2G platinum-based combination regimens (Table 4).[16–19] These trials ranged in size from 53 to 406 patients.

TABLE 3. Homogeneity and Publication Test Results

Comparison	Homogeneity *p* Value	Begg and Mazumdar[14] *p* Value	Sterne et al[15] *p* Value
3G vs. BSC survival			
Overall survival	0.4	1.0	0.7
Single-agent 3G vs. 2G platinum based			
Response	0.5	0.5	0.7
Overall survival	0.3	0.5	0.3
3G platinum based vs. 2G platinum based			
Response	0.2	0.3	0.1
Overall survival	0.1	0.2	0.3

3G, third generation; 2G, second generation; BSC, best supportive care.

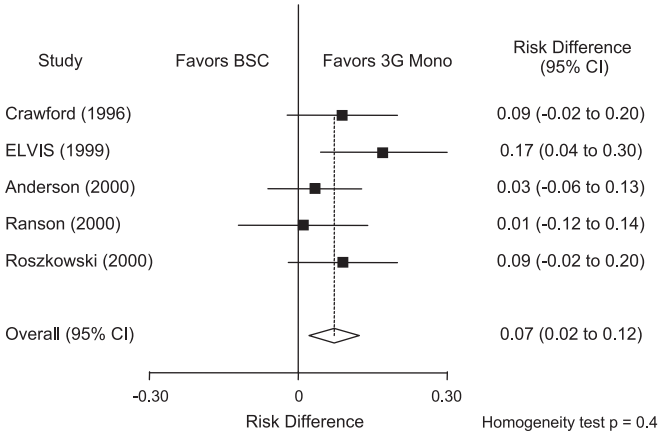


FIGURE 2. Third-generation agents compared with best supportive care. Differences in 1-year survival proportions.

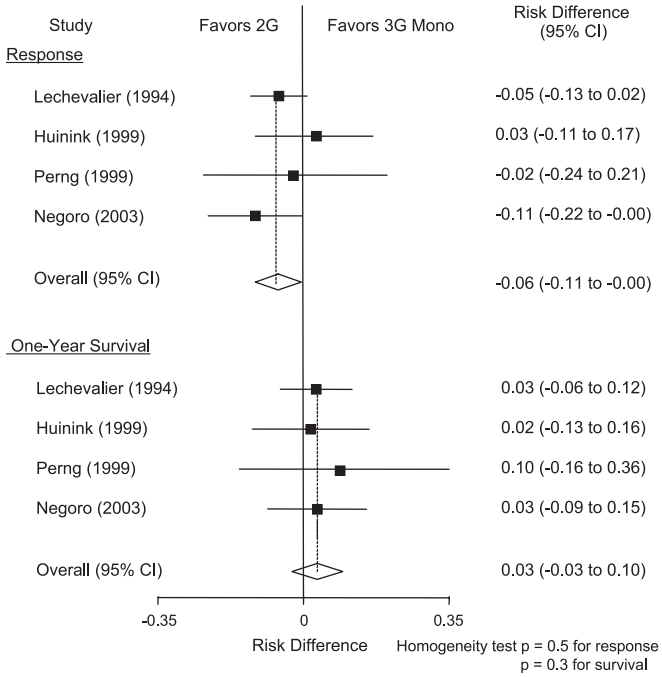


FIGURE 3. Third-generation single agents compared with second-generation platinum-based regimens. Differences in response and 1-year survival proportions.

Two trials were three-arm trials, and the relevant data from the 3G monotherapy and the 2G treatment arms were extracted from these trials.[16,19] There was no evidence of heterogeneity or publication bias (Table 3). The summary RD estimate for response was −6% (95% CI: −11%, 0%), and for 1-year survival rate was 3% (95% CI: −3%, 10%). Despite a suggestion of greater response for the 2G regimens, the RD for survival was close to the null value, suggesting that there is no difference in efficacy between 3G monotherapy and 2G platinum-based combined regimens (Figure 3).

Twelve trials (n= 3995 patients) compared 3G combination regimens including platinum-based compounds with 2G platinum-based regimens (Table 5).[16,19–29] These trials ranged in size from 92 to 572 patients. Two trials were three-arm trials, and the relevant data related to 3G combination and 2G combination treatments were extracted.[16,19] One trial compared a 2G combination against a 3G combination using two different doses of paclitaxel; for that trial, the data from the two paclitaxel arms were combined.[25] For response, there was no evidence of heterogeneity or publication bias (Table 3). The estimated RD was 12% (95% CI: 10%, 15%), corresponding to an NNT of eight for one patient to benefit (Figure 4). For 1-year survival (Figure 5), there was a high degree of heterogeneity among the studies, as evidenced by the homogeneity p value of 0.10, which raises concerns about the validity of combining data from these trials.

DISCUSSION

This meta-analysis clearly demonstrates that 3G monotherapy improves 1-year survival in comparison with BSC. It should be noted that one of these trials, the Elderly Lung

TABLE 4. Third-Generation Single Agents Compared with Second-Generation Platinum-Based Regimens

					Survival	
First Author	Therapy	Number of Patients	Patients Assessable	Overall Response Rate (%)	No. of Patients	1-yr Survival (%)
Le Chevalier*[16]	Vinorelbine	206	199	14	206	30
	Cisplatin, vindesine	200	183	19	200	27
ten Bokkel Huinink[17]	Gemcitabine	72[a]	59	20	67[b]	25
	Cisplatin, etoposide	75[a]	62	18	72[b]	24
Perng[18]	Gemcitabine	27	26	19	27	41
	Cisplatin, etoposide	26	24	21	26	31
Negoro*[19]	Irinotecan	132	127	20	129	42
	Cisplatin, vindesine	133	120	32	122	38

[a] Patients randomized; [b] patients eligible after randomization. *The relevant data from two three-arm trials were extracted and used in the comparison of 3G monotherapy versus 2G platinum-based therapy. Data are not shown for the treatment arm of cisplatin/vinorelbine in the trial by Le Chevalier et al.[16] or for the treatment arm of cisplatin/irinotecan in the trial by Negoro et al.[19]

TABLE 5. Third-Generation Platinum-Based Regimens Compared with Second-Generation Platinum-Based Regimens

					Survival	
First Author	Therapy	Number of Patients	Patients Assessable	Overall Response Rate (%)	No. of Patients	1-yr Survival (%)
Le Chevalier*[16]	Cisplatin, vinorelbine	206	192	30	206	34
	Cisplatin, vindesine	200	183	19	200	27
Baldini[20]	Carboplatin, vinorelbine	43	43	14	43	16
	Cisplatin, vindesine, mitomycin	49	49	14	49	18
Giaccone[21]	Cisplatin, paclitaxel	155[b]	141	45	166[a]	41
	Cisplatin, teniposide	162[b]	141	32	166[a]	40
Wozniak[22]	Cisplatin, vinorelbine	209	206	26	206	36
	Cisplatin	206	209	12	209	20
Cardenal[23]	Cisplatin, gemcitabine	69	69	41	69	32
	Cisplatin, etoposide	64[b]	64	22	64	27
Crino[24]	Cisplatin, gemcitabine	155	155	38	155	33
	Cisplatin, mitomycin, ifosfamide	152	152	26	152	34
Bonomi[25]	Cisplatin, high-dose paclitaxel	191	381	27	381	39[c]
	Cisplatin, low-dose paclitaxel	190				
	Cisplatin, etoposide	193	193	12	193	32
Gatzemeier[26]	Cisplatin, paclitaxel	207	190	26	207	30
	Cisplatin	207	197	17	207	36
Sandler[27]	Cisplatin, gemcitabine	260	245	32	260	39
	Cisplatin	262	240	12	262	28
Gebbia[28]	Cisplatin, vinorelbine	122	122	39	122	15
	Cisplatin, vindesine, mitomycin	125	125	42	125	15
Negoro*[19]	Cisplatin, irinotecan	133	126	44	129	47
	Cisplatin, vindesine	133	120	32	122	38
Kubota[29]	Cisplatin, docetaxel	151	151	37	151	48
	Cisplatin, vindesine	151	151	21	151	41

[a] Patients randomized; [b] patients eligible after randomization; [c] patients in the high-dose and low-dose paclitaxel groups combined. 3G, third generation; 2G, second generation; RCT, randomized controlled trials. *The relevant data from two, three-arm trials were extracted and used in the comparison of 3G platinum-based versus 2G platinum-based regimens. Data are not shown for the treatment arm of single-agent vinorelbine in the trial by Le Chevalier et al.[16] or for the treatment arm of single irinotecan in the trial by Negoro et al.[19]

Cancer Vinorelbine Italian Study,[8] consisted of patients age ≥70 years, and nearly a quarter of the patients had a performance status of 2. Treatment with vinorelbine was superior to BSC on this trial; nevertheless, the data on the efficacy of single-agent vinorelbine may be underestimated because of the patient selection on the trial. The inclusion of the data from 5-FU/leucovorin (LCV) arm as best supportive care from the trial by Crawford et al.[7] may be debatable. Nevertheless, the response and survival on that arm were similar to the BSC arm on other trials, and 5-FU/leucovorin is not considered an active or standard therapy for advanced NSCLC; thus, we feel the inclusion of this trial was justifiable.

Other meta-analyses of older agents have revealed a survival benefit of chemotherapy over BSC.[30,31] Whereas response is undefined in supportive care, response rates for the 3G single agents ranged from 13% to 20%, which is consistent with a recent meta-analysis that have found the response rates of single-agent chemotherapy to be 13%.[32] A systematic review by Sorenson et al.[33] of chemotherapy in advanced NSCLC has revealed that treatment with single-agent paclitaxel, docetaxel, or vinorelbine provided a survival benefit over BSC comparable with older, cisplatin-based combinations.

Our analysis suggests that treatment with 3G monotherapy compared with 2G platinum-based combination therapies yields similar 1-year survival, despite a slightly lower response rate with 3G monotherapy. 3G monotherapy may actually be preferable to 2G combination regimens, because single-agent therapy generally has a lower rate of grade 3 and 4 toxicity than double-agent therapy.[32] A meta-analysis by Lilenbaum et al.[34] investigated the effects of single-agent versus combination chemotherapy on response rate, toxicity, and survival. This meta-analysis found superior response rate and a modest improvement in the 6-month and 1-year survival rates with combination therapy. Nevertheless, when a platinum agent or vinorelbine was used as a single agent, the differences in 6-month and 1-year survival were no longer significant. Combination therapy was associated with a 3.6-fold increase in the risk of treatment-related death, and significantly greater toxicity.

The inclusion of single-agent cisplatin as a 2G regimen may be debatable; nevertheless, single-agent cisplatin was

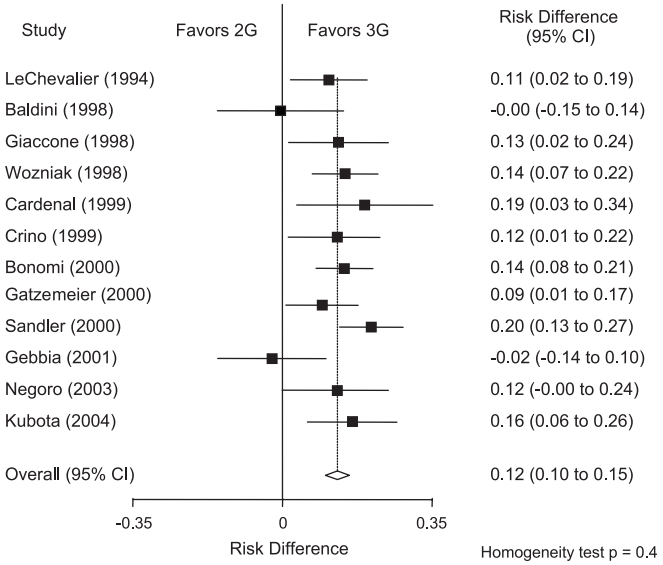


FIGURE 4. Third-generation platinum-based regimens compared with second-generation platinum based regimens. Differences in response proportions.

considered an acceptable comparator arm at the time these trials were performed. A meta-analysis from 52 trials that enrolled 9837 patients, published in 1995, determined that cisplatin-based chemotherapy produced a 10% improvement in 1-year survival over BSC.[35] Because two thirds of the cisplatin-based regimens included a vinca alkaloid or etoposide, it could not be determined whether cisplatin, the other drugs, or both were responsible for the improvement in survival. The meta-analysis by Lilenbaum et al.[34] found that treatment with single-agent platinum analogue had a similar survival to combination therapy as well. A randomized trial of cisplatin versus cisplatin and etoposide demonstrated equivalent response rates and survival between the two treatments.[36] These data suggest that single-agent cisplatin is not a significantly inferior therapy to other 2G regimens.

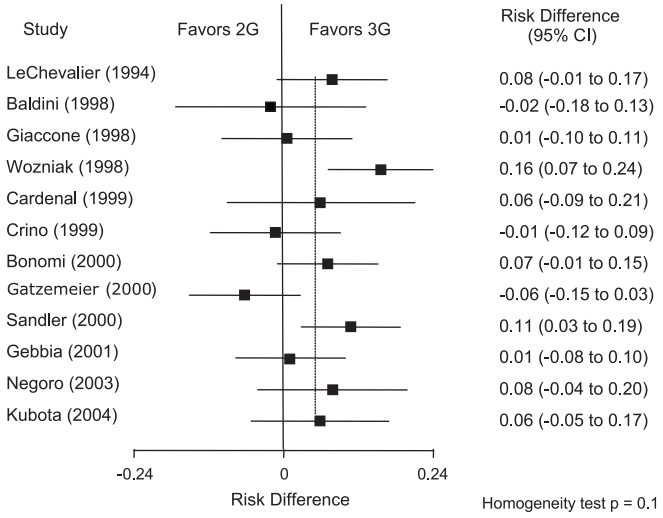


FIGURE 5. Third-generation platinum-based regimens compared with second-generation platinum-based regimens. Differences in 1-year survival proportions.

Treatment with 3G combination therapy resulted in an improvement in the efficacy parameter of response in comparison to 2G platinum-based regimens. Because of concerns about the heterogeneity of the trials, a summary RD could not be estimated reliably on the basis of a p value of 0.06 on the test for homogeneity. A similar meta-analysis by Le Chevalier et al.[37] compared gemacitabine and, in combination with platinum agent versus first-generation and 2G platinum-based comparator regimens, found significant heterogeneity ($p=0.032$) as well. The estimated RD for 1-year survival for this comparison was 5% (95% CI: 2%, 8%), corresponding to an NNT of 20 for one additional patient to survive 1 year after diagnosis. These estimates should not be considered definitive evidence of a survival advantage for 3G combination therapies over 2G platinum-based regimens but, rather, as hypothesis generating.

The use of publication-based data rather than individual patient data may have limited the ability to explore the contributions of specific patient characteristics to the heterogeneity. It is possible that there were significant differences in the percentage of patients receiving second-line therapies among the trials, resulting in differences in overall survival. For instance, the trial by Gatzemeier et al.[26] compared a 2G regimen cisplatin (100 mg/m^2) against a 3G regimen of cisplatin (80 mg/m^2) and paclitaxel (175 mg/m^2) every three weeks. The 3G regimen had a significantly higher response rate (26% versus 17%, respectively; $p = 0.028$), but there were no statistically significant differences in median time to tumor progression (4.1 versus 2.7 months; respectively; $p = 0.26$) or median survival (8.1 versus 8.6 months, respectively; $p = 0.826$). More patients on the cisplatin arm received second-line therapy.

The inclusion of single-, double-, and triple-agent therapies into the broad classification of 2G regimens seems to have contributed to the heterogeneity as well. Within the category of 2G regimens three trials used single-agent cisplatin, six trials used cisplatin in combination with a second agent, and three trials used three-agent therapy. When viewing these trials in aggregate, there is significant heterogeneity. Nevertheless, a subgroup analysis demonstrates excellent homogeneity of results in the individual comparisons of 3G regimens to 2G doublets and 3G regimens compared with 2G triplets. A summary statistic could not reasonably be generated for the comparison of 3G regimens with 2G single agents, because of considerable heterogeneity ($p = 0.001$). In contrast, excellent consistency of study results was observed among the six trials comparing 3G regimens against 2G doublets (homogeneity p value = 0.93). This comparison reveals a 1-year overall survival RD of 6% (95% CI: 2%, 10%), favoring 3G regimens over 2G doublets (Figure 6). Excellent consistency was also observed among the three trials comparing 3G regimens against 2G triplet combinations (homogeneity p value = 0.91). Nevertheless, an RD of 0% (95% CI: −7%, 6%) indicates no difference in the estimated 1-year overall survival between 3G regimens and 2G triplets.

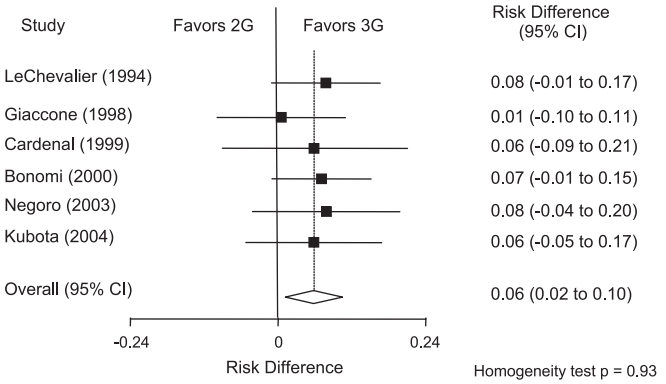


FIGURE 6. Third-generation platinum-based regimens compared with second-generation platinum doublet regimens. Differences in 1-year survival proportions.

Several other studies have investigated the efficacy of 3G agents. A previous systematic review revealed an improvement in survival for treatment with cisplatin and a 3G agent (defined as gemcitabine, paclitaxel, irinotecan, and vinorelbine) versus treatment with cisplatin and a 2G agent.[33] A meta-analysis by Le Chevalier et al.[37] that specifically investigated the efficacy of the 3G agent gemcitabine found an improvement in progression-free survival and overall survival for treatment with platinum-based therapy with gemcitabine, over 2G platinum-based combinations. A second meta-analysis of eight trials (2425 patients) compared treatment with cisplatin and a 3G agent (defined as taxanes, vinorelbine, gemcitabine, and irinotecan) against treatment with cisplatin and a 2G agent (defined as vindesine, etoposide, teniposide, mitomycin C, and ifosfamide), revealing superior response and survival with cisplatin and a 3G agent.[38] These studies indicate that the 3G agents have been a significant advance in the treatment of NSCLC.

There are several weaknesses of this meta-analysis. We did not investigate differences in the rate and severity of treatment-related toxicity or quality of life between treatment with 3G agents and previous therapies. Rather, the goal of this meta-analysis was to assess the impact of 3G on efficacy parameters. A separate meta-analysis evaluating these issues would be a valuable addition to the literature. Another limitation is the potential influence of publication bias. Although the two tests that were conducted to address this issue produced little or no evidence of publication bias, the small number of trials limited the power of these tests. The strengths of this meta-analysis are that it specifically evaluates three different clinical scenarios, and two frequently used efficacy endpoints.

The use of response as an endpoint is open to question because differences in response between two treatments may not translate into differences in survival. For instance, for the comparison of 3G monotherapy versus 2G platinum-based regimens, the response comparison suggested a higher response rate for 2G platinum-based therapy, but the 1-year survival rate was equivalent between 3G monotherapy and the 2G platinum-based regimens; this strongly supports that these agents have improved therapy for the treatment of advanced NSCLC. Nevertheless, response rate is frequently used as an efficacy endpoint for many phase II trials evaluating new agents or combinations, and the estimation of the response rate with previous regimens from a meta-analysis may assist in the development of future clinical trials.

There is currently no standard chemotherapy combination for advanced NSCLC, and the American Society of Clinical Oncology guidelines recommend treatment with double-agent chemotherapy for patients with advanced disease and good functional status.[5] The standard therapy for many physicians and oncology cooperative groups is a 3G agent in combination with a cisplatin or carboplatin. Nevertheless, there has been development of several "targeted" therapies, multitargeted tyrosine kinase inhibitors, and new cytotoxic chemotherapy agents that have shown activity in advanced NSCLC since the development of the 3G agents. Bevacizumab in combination with carboplatin and paclitaxel has demonstrated an improvement in survival in a select group of first-line patients.[39] In the second-line setting, erlotinib (an epidermal growth factor receptor tyrosine kinase inhibitor) and pemetrexed (a multitargeted antifolate) have demonstrated activity in patients who have progressed after first-line therapy as well in phase III trials.[40,41] The multitargeted tyrosine kinase inhibitors (suntinib, sorafenib, ZD6474) have demonstrated activity in phase II trials in patients experiencing progression after first-line therapy.[42–44] Many of these new agents have been or will be integrated into 3G combination therapies for patients with preserved functional status, or they may be integrated with single 3G agents for elderly patients or those with marginal functional status. Thus, 3G agents will continue to have a major role in the treatment of advanced NSCLC.

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