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REVIEW

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Chemotherapy: the more the better? Overview

Abstract Although numerous clinical trials of high-dose chemotherapy have been performed, few have demonstrated that such strategies are statistically significantly better than other forms of therapy. Application of dose-intensive and/or high-dose chemotherapy should be limited to drug-sensitive tumors, with primary end points being increased cure rates or prolonged survival. This should be confirmed by randomized clinical trials comparing dose-intensive and/or high-dose chemotherapy with standard therapeutic modalities.

Key words Dose-intensive chemotherapy · High-dose chemotherapy · Drug resistance

Introduction

The results of the use of conventional cytotoxic therapy to treat common solid tumors have not improved greatly in recent years. The main cause of this failure is inherent and acquired drug resistance, strategies for overcoming which include the use of non-cross-resistant drugs [10], modulators of drug resistance, and different modalities such as radiation therapy or surgery; the use of new categories of anticancer drugs is also a possible strategy. Dose-intensive and/or high-dose chemotherapy is a complementary strategy for overcoming drug resistance [18–23].

It is well known that reducing the chemotherapy dose reduces the response rate and does not cure cancer [12]. However, a major question is whether increases in the dose intensity of chemotherapy will produce significant improvements in outcome for patients with common malignancies [46, 51].

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Rationale for dose intensification

The rationale for the hypothesis of dose-intensive chemotherapy is as follows. Dose-response relationships exist when drugs are used at doses above the conventional range, and such relationships are quantitatively sufficient to produce a substantial increase in response, which improves survival. Chemotherapy can be intensified by (1) intensifying conventional treatment using hematopoietic growth factors; (2) giving a restricted number of cycles of high-dose treatment with peripheral blood stem-cell and hematopoietic growth factor support; and (3) giving single very-high-dose chemotherapy with peripheral blood stem-cell or bone marrow transplantation and hematopoietic growth factor support. These procedures are usually used for late intensification or as initial treatment.

End points

Appropriate end points for assessing the benefit of dose-intensive and high-dose chemotherapy are overall survival and quality of life. Thus, whether dose-intensive chemotherapy can change the goal of treatment from palliation to cure becomes relevant. If it can, the associated toxicity and/or cost are acceptable. If it cannot, the optimal dose and/or dose intensity for optimal palliation should be determined. The drug-induced toxicity and response rates increase according to the dose, whereas the improvement in palliation follows a bell-shaped curve. This suggests that chemorefractory tumors such as non-small-cell lung cancer (NSCLC), colon carcinoma, and stomach cancer are not candidates for dose-intensive chemotherapy.

Another end point of dose-intensive chemotherapy is tumor shrinkage or response [16]. However, patient selection and response criteria influence the response rate more

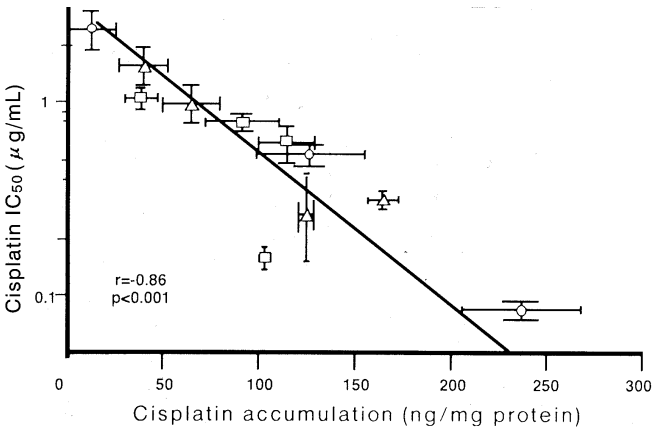

Fig. 1 Cisplatin IC_{50} values in various NSCLC cell lines

than do the drugs and doses used. Thus, tumor response is at best only a surrogate end point for patient benefit.

Dose increment

Another key question addresses how much the dose must be intensified to obtain meaningful benefit. Within and below the standard dose range the dose-response relationship is steep, but it may tend to plateau above the usual range. Basic data on drug resistance suggest that an increase in dose on the order of 5- to 10-fold is necessary for a move into the curative range.

Nonhematological toxicity sometimes prevents necessary drug concentrations from being attained. Figure 1 shows the 50% growth-inhibitory concentrations (IC_{50} values) determined for cisplatin in various NSCLC cell lines (cell lines with acquired resistance are not included). The IC_{50} values noted for some cell lines was <0.1 μg/ml, whereas that recorded for others was >1.0 μg/ml, and there was a $\geq$10-fold difference in sensitivity for each cell line [36]. Table 1 shows the characteristics of cell lines with acquired resistance to topoisomerase I inhibitors. Relative resistance values range from 2 to 500. As it is impossible to achieve an extremely high concentration of topoisomerase I inhibitors, another strategy is needed to overcome resistance. However, the IC_{50} values shown for 6 of these 12 cell lines lie within a 10-fold concentration range. Such concentrations can be achieved using high-dose chemotherapy [43].

Essential clinical trials

What is a meaningful improvement in outcome? If small but definitive improvements in cure rate are obtained, the improvement would be considered beneficial, whereas improvements in response rate and palliation are regarded as outcomes of lower priority, even if the gain is large.

Clinical trials of dose-intensive chemotherapy can be classified on the basis of their quality. The highest priority should be given to repeated, large, randomized, controlled trials or meta-analyses followed by single, small-scale, randomized controlled trials; trials using historical controls; and, finally, case series [41]. In comparisons among patients treated in different clinical trials, prognostic factors and/or cancer stage strongly influence the outcome in addition to dose and/or dose intensity [4].

Patients with favorable prognostic factors such as localized disease are more suitable for evaluation of the effect of dose-intensive chemotherapy on survival. The highest level of evidence should come from large, randomized, controlled trials in which the only factor varied is the dose or dose intensity of chemotherapy. Very few studies with such a design have been completed and controversial results have been obtained, i.e., some reports show little improvement and others no effect. However, in the majority of studies the difference in dose intensity has been very small.

Table 1 Characteristics of cell lines with acquired resistance to topoisomerase I inhibitors (*RR* Relative resistance, *Topo I* topoisomerase I, *CPT-11* irinotecan, *CPT* camptothecin, *NB-506* an indolocarbazol derivative, *CHO* Chinese hamster ovary cell, *T-ALL* T-cell acute lymphoblastic leukemia, *CHL* Chinese hamster lung cell, *R* resistant, *S* sensitive, *ND* not determined)

Cell line[a]	Selecting agent	Origin	RR	Topo I concentration (μg)	Topo I sensitivity to CPT	Gene alteration
PC-7/CPT	CPT-11	Human lung cancer	9	0.25	R	+ Mutation
HAC-2/CPT	CPT-11	Human ovarian cancer	9.7	0.5	0.5	–
SBC-3/NB	NB-506	Human lung cancer	454	0.1	S	–
CPT-K5	CPT-11	Human T-ALL	300	0.3–0.5	R	+ Mutation
CPT-B	CPT	CHO	250–300	0.4–0.5	R	ND
HT-29/CPT	CPT	Human colon cancer	7	0.13	S	+ Deletion
A549/CPT	CPT	Human lung cancer	2	1.0	ND	ND
St-4/CPT	CPT	CHL	9	0.25	ND	ND
DC3F/C10	CPT	CHL	134	1.0	R	+ Mutation
V79	CPT	CHL	14	0.25	ND	
IRS-1	CPT	CHL	2	0.1	S	
IRS-2	CPT	CHL	34	0.5	R	

[a] PC-7/CPT-11, HAC-2/CPT11, and SBC-3/NB were developed at the National Cancer Center Research Institute

Table 2 Randomized clinical trials of dose-intensive chemotherapy in breast cancer. Modified and reproduced with permission from Takifuji and Fukuoka [50] (*CPA* Cyclophosphamide, *MTX* methotrexate, *5FU* 5-fluorouracil, *ADM* doxorubicin, *RR* relative risk, *TTR* time to relapse, *DFS* disease-free survival)

Drugs studied	Number of patients	Dose or dose intensity (mg/m^2)	Outcome (low vs high dose)	Reference
DPA, MTX, 5FU	133	300, 20, 300 vs 600, 40, 600	RR: 11% vs 30% ($P = 0.03$)	[52]
Epirubicin	218	40 vs 60 vs 90 vs 135	RR, TTR: 40 or 60 < 90 or 135	[3]
CPA, ADM, 5FU	1529	150, 15, 300 vs 100, 10, 200 vs 75, 7.5, 150	Survival: moderate ($P < 0.001$) DFS: moderate ($P < 0.004$)	[54]

Example

The chemotherapy dose intensity and the percentage of survival have also been shown to be positively correlated in a review of a trial of treatment for aggressive lymphoma [8]. However, the increases in dose intensity achieved in this trial were <2.5-fold enhancements, the analysis was retrospective and designed for an independent uncontrolled study, and these conclusions have not subsequently been supported by the results of large, randomized, controlled trials.

Randomized controlled trials of dose-intensive chemotherapy have been conducted for breast cancer [7, 17, 52, 54]. The trials conducted by Tannock et al. [52], Bastholt et al. [3], and Wood et al. [54] suggest that the outcome is better in high-dose groups (Table 2). However, the high-dose group in these trials did not receive high-dose chemotherapy and the dose given to the control group was inappropriately low. In addition, randomized controlled trials conducted at other institutions have revealed no association between dose and outcome [3, 4].

The results obtained using dose-intensive chemotherapy in ovarian cancer are controversial [1, 6, 9, 12, 26, 28–31, 38]. Although the cisplatin dose was almost doubled in the high-dose group in each of these trials, no significant difference in complete or objective response rate and survival was found between the high- and conventional-dose groups (Table 3).

The situation for dose-intensive chemotherapy in testicular cancer is similar [39, 40, 44] (Table 4). Of three randomized trials comparing the cisplatin dose, only one [44] demonstrated a survival benefit for high-dose chemotherapy. The study by Ozols et al. [40] showed a marginal benefit for high-dose chemotherapy, but that reported by Nichols et al. [39] showed no benefit.

Table 3 Randomized clinical trials of dose-intensive chemotherapy in ovarian cancer. Modified and reproduced with permission from Takifuji and Fukuoka [50] (*RR* Relative risk, *MST* median survival time, *NS* not significant)

Number of patients	Dose intensity[a]	Total dose[a]	Outcome (low vs high dose)	Reference
50	×2	×2	3-year survival: 30% vs 60%	[38]
165	×2	×2	MST: low < high ($P < 0.0008$)	[26]
296	×2	×1	RR, MST: NS	[6]
458	×1.97	×1	RR, MST: NS	[31]

[a] The dose intensity and the total dose of the high-dose therapy in relation to low-dose therapy are indicated

No effect of high-dose chemotherapy on response rate or survival in small-cell lung cancer has been revealed [13, 14, 16, 25, 27, 33–35, 37, 42, 45, 47, 53] (Table 5). However, in these studies the patient population was small and the chemotherapeutic agents used in the majority of cases were not state-of-the-art compounds [2]. Only one trial compared high and low doses of cisplatin with etoposide, but the results did not show any benefit of high-dose therapy [24]. Only a marginal benefit of dose-intensive cisplatin, vincristine, doxorubicin, and etoposide (CODE) therapy over treatment with cyclophosphamide, doxorubicin, and vincristine (CAV) and alternating cisplatin and etoposide (PVP) was revealed by the Japanese Clinical Oncology Group [15]. There are limitations to many of these studies, including excessively small sample sizes that detect only modest differences, a lack of data on the received dose intensity, and, often, a lack of survival data [2].

Table 4 Randomized clinical trials of dose-intensive chemotherapy in testicular cancer. Modified and reproduced with permission from Takifuji and Fukuoka [50] (*CDDP* cisplatin, *VLB* vinorelbine, *BLM* bleomycin, *CR* complete response rate, *MST* median survival time, *NR* no response, *DFS* disease-free survival, *RR* relative risk, *NS* not significant)

Drugs studied	Number of patients	Dose or dose intensity (mg/m^2)	Outcome (low vs high dose)	Reference
CDDP (+VLB and BLM)	114	19 vs 30/week	CR: 43% vs 60% ($P = 0.03$) Survival low < high	[44]
CDDP (+VLB, BLM, and etoposide)	52	100 vs 200	MST: 30 months vs NR 5-year survival: 48% vs 78% ($P = 0.06$)	[40]
CDDP (+BLM and etoposide)	153	100 vs 200	RR, survival: NS	[39]

Table 5 Randomized clinical trials of dose-intensive chemotherapy in small-cell lung cancer. Modified and reproduced with permission from Takifuji and Fukuoka M [50] (*CCNU* Carboplatin, *CPA* cyclophosphamide, *MTX* methotrexate, *DOX* doxorubicin, *VP-16* etoposide, *VCR* vincristine)

Drug	Dose/m²	Arm	*n*	Response		Mean response duration	Survival
				Complete	Partial		
CCNU CPA MTX	100 ng 1 g 15 mg	High	23	7	15	10.5	7 alive at 1 year
CCNU CPA MTX	50 mg 500 mg 10 mg	Low	9	0	4	5.0	1 alive at 1 year
MTX	6 g	High	19	4	14	9	2 alive at 18 months
MTX	20 mg	Low	21	5	15	9	2 alive at 18 months
DOX VCR CPA VP-16	40 mg 1 mg 1 g 180 mg×3	Both groups					
PLAT VP-16	135 mg 80 mg×5	High	40	10	24	12	52% at 1 year
PLAT VP-16	80 mg 80 mg×3	Low	43	8	25	11	47% at 1 year
CPA DOX	1.5 g 60 mg	High	52	11	26	10–12	25% at 18 months
CPA DOX	1 g 50 mg	Low	51	11	20	10–12	20% at 18 months
CPA DOX	1.2 g 70 mg	High		54	64	14	–
			Total 45				
CPA DOX	750 mg 50 mg	Low		30	55	9	–
VCR in both							

In addition to the problems associated with comparison of different trials, subjective interpretation of data from the same trial by different researchers can also create problems. The resolution of some of these issues awaits the results of large-scale trials of high-dose intensive chemotherapy with hematopoietic growth factor support.

Single high-dose therapy with hematopoietic stem-cell support

If a modest increase in chemotherapy intensity does not increase the cure rate significantly, it is nonetheless possible that treatment with 5- to 10-fold the conventional dose might eliminate residual tumor. This dose can be achieved with peripheral blood stem-cell transplantation or autologous bone marrow transplantation with hematopoietic growth factor support. Such support reduces the duration of neutropenia to 8–14 days, and mortality is reduced to 1–3%.

Incomplete responders to conventional treatment are likely to show a further response after high-dose therapy for germ-cell tumors, small-cell lung cancer, ovarian cancer, and lymphoma [48]. In breast cancer, encouraging results obtained in an uncontrolled phase II study have indicated that the complete response rate is increased by high-dose chemotherapy and that the response continues, although the duration of this response is usually short. The benefit of this strategy is now the subject of randomized controlled trials.

For small-cell lung cancer, data obtained in uncontrolled phase II studies are encouraging, with Elias et al. [11] reporting a high 2-year survival rate. However, patient selection is a significant problem in the evaluation of single-arm phase II studies. Recently, the Japanese Clinical Oncology Group presented promising data for concurrent chemotherapy using cisplatin plus etoposide with twice-daily irradiation [49]; the median survival in their study was approximately 30 months. Further randomized trials to evaluate the effect of high-dose chemotherapy should be initiated to confirm these results. Potential problems associated with early phase II studies of high-dose therapy against small-cell lung cancer have included inadequate chemotherapy, usually with a single agent and an alkylating agent, the use of patients with advanced disease and partial responders, and inappropriate radiation strategies and a lack of chest or cranial irradiation.

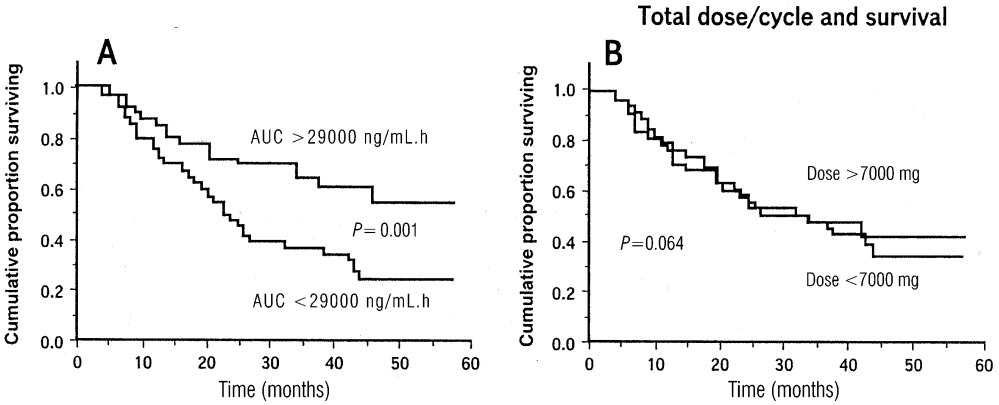

Fig. 2A, B Correlation between **A** the average AUC/cycle of 5-fluorouracil and survival and **B** the total 5-fluorouracil dose/cycle and survival. Reproduced with permission from Milano et al. [32]

Adjuvant chemotherapy

Full-dose active chemotherapy is essential during adjuvant chemotherapy. However, definitive data favoring the use of hematopoietic growth factor to maintain dose intensity are not available. This issue should be addressed in randomized controlled trials.

Pharmacokinetics and pharmacodynamics studies

Whether pharmacology studies should be used as a guide for high-dose chemotherapy is an important question, with pharmacokinetics studies being complementary to clinical studies. Simple measurements of plasma drug concentrations are inadequate, and pharmacodynamic analysis is crucial [5]. Drug penetration into tumors, the steepness of the dose-response curve, and the development of drug resistance should also be considered.

Figure 2 shows the correlation between the pharmacokinetics of 5-fluorouracil and survival and indicates that patients with higher AUC values survive longer than those with lower values [32]. This was not a study of high-dose chemotherapy but rather a retrospective analysis of pharmacokinetics and outcome. This kind of study is essential in the evaluation of high-dose chemotherapy. The drug administration schedule and circadian rhythms are also important factors in the determination of response. However, even on an optimal schedule the dose and the dose intensity may influence the outcome.

Conclusions

Numerous studies on high-dose intensive chemotherapy have been conducted, but there is nonetheless little evidence to confirm that high-dose intensive chemotherapy is beneficial. Although this review is generally critical, physicians and patients need to fight cancer. Therefore, we wish to stress that high-dose and/or dose-intensive chemotherapy can attain a state-of-the-art position only on the basis of evidence obtained from large, randomized controlled trials.

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References

1. Arbuck SG, Blaylock BA (1995) Dose and schedule issues in paclitaxel in cancer treatment. In Paclitaxel in cancer treatment, McGuire WP, Rowinsky EK (eds) Marcel Dekker, New York, p 151
2. Arriagada R, Le Chevalier T, Pignon JP, Riviere A, Monnet I, Chomy P, Tuchais C, Tarayre M, Ruffie P (1993) Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. N Engl J Med 329:1848
3. Bastholt L, Dalmark M, Gjedde S, Pfeiffer P, Petersen D, Sandberg E, Kjaer M, Mouridsen HT, Rose C, Nielsen OS, Jakobsen P (1992) Epirubicin at four different dose levels in metastatic breast cancer. A randomized trial. Proc Am Soc Clin Oncol 11:56A
4. Bull JM, Tormey DC, Li SH, Carbone PP, Falkson G, Blom J, Perlin E, Simon R (1978) A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer 41:1649
5. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748
6. Colombo N, Pitteli MR, Parma G, Marzola M, Torri W, Mangioni C (1993) Cisplatin (P) dose intensity in advanced ovarian cancer (AOC): a randomized study of conventional dose (DC) vs dose-intense (DI) cisplatin monochemotherapy. Proc Am Soc Clin Oncol 12:255
7. Cooper RG, Holland JF, Glidewell O (1979) Adjuvant chemotherapy of breast cancer. Cancer 44:793
8. DeVita VT, Hubbard SM, Longo DL (1987) The chemotherapy of lymphomas: looking back, moving forward – the Richard and Linda Rosenthal Foundation Award Lecture. Cancer Res 47:5810
9. Eisenhauer EA, Bokkel Huinink WW ten, Swenerton KD, Gianni L, Myles J, Burg ME van der, Kerr I, Vermoken JB, Buser K, Colombo N, Bacon M, Santabárbara P, Onetto N, Winograd B, Canetta R (1994) European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. J Clin Oncol 12:2654
10. Einzig AI, Wiemik PH, Sasloff J, Runowicz CD, Goldberg GL (1992) Phase II study and long-term follow-up of patients treated with Taxol for advanced ovarian adenocarcinoma. J Clin Oncol 10:1748

11. Elias AD, Ayash L, Frei E, Skarin AT, Hunt M, Wheeler C, Schwartz G, Mazanet R, Tepler I, Eder JP, McCauley M, Herman T, Schnipper L, Antman KH (1993) Intensive combined modality therapy for limited-stage small-cell lung cancer. J Natl Cancer Inst 85:559
12. Frei E III, Canellos GP (1980) Dose: a critical factor in cancer chemotherapy. Am J Med 69:585
13. Fukuoka M, Furuse K, Saijo N, Nishiwaki Y, Ikegami H, Tamura T, Shimoyama M, Suemasu K (1991) Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst 83:855
14. Fukuoka M, Masuda N, Takeda M Kodama N, Kawahara M, Furuse K (1994) Chemotherapy in extensive-stage small-cell lung cancer. Semin Oncol 21[Suppl 1]:43
15. Furuse K, Kubota K, Nishikawa Y, Takada M, Kurita Y, Watanabe K, Noda K, Fukuoka M, Ariyoshi H, Osaki Y, Tamura H, Saijo N, for the Japan Lung Cancer Study Group (1996) Phase II study of dose intensive weekly chemotherapy with recombinant human granulocyte-colony stimulating factor (G-CSF) versus standard chemotherapy in extensive stage small-cell lung cancer (SCLC). Proc Am Soc Clin Oncol 15:375
16. Giaccone G, Dalesio O, McVie GJ, Kirkpatrick A, Postmus PE, Burghouts JT, Bakker W, Koolen MG, Vendrik CP, Roozendaal KJ, Planting AST, Zandwijk N van, Velde GJM ten, Splinter TAW, for the European Organization for Reasearch and Treatment of Cancer Lung Cancer Cooperative Group (1993) Maintenance chemotherapy in small-cell lung cancer: long-term results of a randomized trial. J Clin Oncol 11:1230
17. Henderson IC, Hayes DF, Gelman R (1988) Dose response in the treatment of breast cancer: a critical review. J Clin Oncol 6:1501
18. Hryniuk W (1986) Is more better? J Clin Oncol 4:621
19. Hryniuk WM (1987) Average relative dose intensity and impact on design of clinical trials. Semin Oncol 14[Suppl 4]:65
20. Hryniuk W (1995) Will increases in dose intensity improve outcome: pro? Am J Med 99:69S
21. Hryniuk W, Bush H (1984) The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2:1281
22. Hryniuk W, Levine MN (1986) Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. J Clin Oncol 4:1162
23. Hryniuk WM, Figueredo A, Goodyear M (1987) Applications of dose intensity to problems in chemotherapy of breast and colorectal cancer. Semin Oncol 14[Suppl 4]:3
24. Ihde DC, Mulshine JL, Kramer BS, Steinberg SM, Linnoila RI, Gazdar AF, Edison M, Phelps RM, Lesar M, Phares JC, Grayson J, Minna JD, Johnson BE (1994) Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell cancer. J Clin Oncol 12:2022
25. Johnson DH, Einhorn LH, Birch R, Vollmer R, Perez C, Krauss S, Omura G, Greco FA (1987) A randomized comparison of high-dose versus conventional-dose cyclophosphamide, doxorubicin, and vincristine for extensive-stage small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 5:1731
26. Kaye SB, Lewis CR, Paul J, Duncan ID, Gordon HK, Kitchener HC, Cruickshank DJ, Atkinson RJ, Soukop M, Rankin EM, Cassidy J, Davis JA, Reed NS, Crawford SM, MacLean A, Swapp GA, Sarkar TK, Kennedy JH, Symonds RP (1992) Randomized study of two doses of cisplatin with cyclophosphamide in epithelial ovarian cancer. Lancet 340:329
27. Klasa RJ, Murray N, Coldman AJ (1991) Dose-intensity meta-analysis of chemotherapy regimens in small-cell carcinoma of the lung. J Clin Oncol 9:499
28. Kohn EC, Sarosy G, Bieher A, Link C, Christian M, Steinberg SM, Rothenberg M, Adamo DO, Davis P, Ognibene FP, Cunnion RE, Reed E (1994) Dose-intense taxol: high response rate in patients with platinum-resistant recurrent ovarian cancer. J Natl Cancer Inst 86:18
29. Levin L, Hryniuk WM (1987) Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. J Clin Oncol 5:756
30. McGuire WP, Rowinsky EK, Rosenshein NB, Grumbine FC, Ettinger DS, Armstrong DK, Donehower RC (1989) Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med 111:272
31. McGuire WP, Hoskins WJ, Brady MF, Homesley HD, Creasman WT, Berman ML, Ball H, Berek JS, Woodward J (1995) Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 13:1589
32. Milano G, Etierme MC, Renee N, Thyss A, Schneider M, Ramaioli A, Demard F (1994) Relationship between fluorouracil systemic exposure and tumor response and patient survival. J Clin Oncol 12:1291
33. Miles DW, Souhami RL, Spiro SG, Rudd RM, Ash CM, Trask CW, James L, Harper PG (1992) A randomized trial comparing "standard" 3 weekly chemotherapy (C/T) in patients (PTS) with small-cell lung cancer (SCLC). Proc Am Soc Clin Oncol 11:289
34. Miles DW, Fogarty O, Ash CM, Rudd RM, Trask CW, Spiro SG, Gregory WM, Ledermann JA, Souhami RL, Harper PG (1994) Received dose-intensity: a randomized trial of weekly chomotherapy with and without granulocyte colony-stimulating factor in small-cell lung cancer. J Clin Oncol 12:77
35. Morikage T, Ohmori T, Nishio K, Fujiwara Y, Takeda Y, Saijo N (1993) Modulation of cisplatin sensitivity and accumulation by amphotericin B in cisplatin-resistant human lung cancer cell line. Cancer Res 53:3302
36. Murray N (1987) The importance of dose and dose intensity in lung cancer chemotherapy. Semin Oncol 14[Suppl 4]:20
37. Murray N, Shah A, Osoba S, Page R, Karsai H, Grafton C, Goddard K, Fairey R, Voss N (1991) Intensive weekly chemotherapy for the treatment of extensive-stage small-cell lung cancer. J Clin Oncol 9:1632
38. Ngan HYS, Choo YC, Cheung M, Wong LC, Ma HK, Collins R, Fung C, Ng CS, Wong V, Ho HC (1989) A randomized study of high-dose versus low-dose cis-platinum combined with cyclophosphamide in the treatment of advanced ovarian cancer. Hong Kong Ovarian Carcinoma Study Group. Chemotherapy 5:221
39. Nichols CR, Williams SD, Lochrer PJ, Greco FA, Crawford ED, Weetlaufer J, Miller ME, Bartolucci A, Schacter L, Einhorn LH (1991) Randomized study of cisplatin dose intensity in poor-risk germ cell tumors: a Southeastern Cancer Study Group and Southwest Oncology Group protocol. J Clin Oncol 9:1163
40. Ozols RF, Ihde DC, Lincham WM, Jacob J, Ostchega Y, Young RC (1988) A randomized trial of standard chemotherapy vs a high-dose chemotherapy regimen in the treatment of poor prognosis nonseminomatous germ-cell tumors. J Clin Oncol 6:1031
41. Piantadosi S, Saijo N, Tamura T (1992) Basic design considerations for clinical trials in oncology. Jpn J Cancer Res 83:547
42. Roth BJ, Johnson DH, Einhorn LH, Schacter LP, Cherng NC, Cohen HJ, Crawford J, Randolph JA, Goodlow JL, Broun GO, Omura GA, Greco FA (1992) Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 10:282
43. Saijo N, Nishio K, Kubota N, Kanzawa F, Shinkai T, Karato A, Sasaki Y, Eguchi K, Tamura T, Ohe Y, Oshita Y, Nishio M (1994) 7-Ethyl-10-4(1-piperidino)-1-piperidinocarbonyloxycamptothecin: mechanism of resistance and clinical trials. Cancer Chemother Pharmacol 342:S112
44. Samson MK, Rivkin SE, Costanzi JJ, LoBuglio AF, Stephens RL, Gehan EA, Cummings GD (1984) Dose-response and dose-survival advantage for high- versus low-dose cisplatin combined with vinblastine and bleomycin in disseminated testicular cancer. A Southwest Oncology Group study. Cancer 53:1029
45. Sheehan RG, Balaban EP, Frenkel EP (1993) The impact of dose intensity of standard chemotherapy regimens in extensive stage small-cell lung cancer. Am J Clin Oncol 16:250
46. Souhami RL (1995) Will increases of dose intensity improve outcome: con? Am J Med 99:71S

47. Spiro SG, Souhami RL, Geddes DM, Ash CM, Quinn H, Harper PG, Tobias JS, Partridge M, Eraut D (1989) Duration of chemotherapy in small-cell lung cancer: a Cancer Research Campaign trial. Br J Cancer 59:578
48. Spitzer G, Spencer V, Dunphy FR (1992) High-dose chemotherapy with autologous bone marrow support for lung cancer. In: Armitage JO, Antman KH (eds) High-dose cancer chemotherapy, pharmacology, hematopoietins, stem cells. Williams and Wilkins, Baltimore, p 719
49. Takada M, Fukuoka M, Furuse K, Ariyoshi H, Ikegami H, Kurita Y, Nishiwaki Y, Nishikawa H, Watanabe K, Noda K, Saijo N, for the JCOG-Lung Cancer Study Group (1996) Phase II study of concurrent versus sequential thoracic radiotherapy (TRT) in combination with cisplatin (C) and etoposide (E) for limited-stage (LS) small-cell lung cancer (SCLC): preliminary results of the Japan Clinical Oncology Group (JCOG). Proc Am Soc Clin Oncol 15:372
50. Takifuji N, Fukuoka M (1996) Dose intensive chemotherapy in current review. In: Tsurso T, Saijo N (eds) Konnichi no Kagakuryoho. Chugai-Igakusha, Tokyo, p 268
51. Tannock I (1995) Will increase in chemotherapy dose intensity improve the outcome of patients with common malignancies? Introduction to discussion. Am J Med 99:68S
52. Tannock IF, Boyd NF, Deboer G, Erlichman C, Fine S, Larocque G, Mayers C, Perrault D, Sutherland H (1988) A randomized clinical trial of two dose levels of cyclophosphamide, methotrexate and fluorouracil chemotherapy for metastatic breast cancer. J Clin Oncol 6:1377
53. Woll PJ, Hodgetts J, Lomax L, Bildet F, Cour-Chabernaud V, Thatcher N (1995) Can cytotoxic dose-intensity be increased by using granulocyte colony-stimulating factor?: a randomized controlled trial of lenograstim in small-cell lung cancer. J Clin Oncol 13:652
54. Wood WC, Budman DR, Korzun AH, Cooper MR, Younger J, Hart RD, Moore A, Ellerton JA, Norton L, Ferree CR, Colangelo Ballow A, Frei E III, Henderson IC (1994) Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 330:1253