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The importance of dose and schedule in chemotherapy for small cell lung cancer

M Ranson and N Thatcher

University of Manchester, CRC Department of Medical Oncology, Christie Hospital NHS Trust, Manchester, UK.

To improve the survival outlook for patients with small cell lung cancer a variety of chemotherapy strategies has been adopted. This review focuses on the evidence for schedule dependency, particularly with regard to etoposide, and reviews the use of alternating chemotherapy protocols and weekly regimens in small cell lung cancer treatment. Recent improvements in supportive care, with the use of haemopoietic growth factors and peripheral blood progenitor cells, have led to renewed interest in the concept of dose intensity. Preliminary results of dose intensification in small cell lung cancer are described and future prospects discussed.

Introduction

Chemotherapy was first recognised as the cornerstone of treatment in small cell lung cancer (SCLC) in 1969 when it was concluded that cyclophosphamide improved the survival of SCLC patients.[1] Combination chemotherapy quickly emerged as being superior to single agents, and within a decade an overview by Bunn was reporting response rates of 77%, complete response rates of 25% and a median survival of 33 weeks.[2]

During the 1970s and early 1980s chemotherapy regimens for SCLC were largely based upon cyclophosphamide, doxorubicin and vincristine. Anecdotal studies during this period suggested that more intensive chemotherapy could improve the response rate, survival, or both,[3,4] but attention was diverted from these findings in the early 1980s when etoposide was identified as an important agent for the treatment of SCLC.[5–7] Though the incorporation of etoposide into chemotherapy regimens did not yield major improvements in outcome, the modest gains in survival confirmed etoposide as an important agent in SCLC.

Cisplatin and etoposide, which demonstrated synergism in animal tumour models,[8] were found to have promising activity as salvage therapy following cyclophosphamide/doxorubicin/vincristine (CAV) therapy.[9] In studies of patients with relapsed or refractory SCLC, the combination of cisplatin and etoposide (PE) gave a median response rate of 47%[10] and PE combinations became increasingly used as initial chemotherapy.[11–14] Response rates to PE in chemo-naive patients have been typically above 70%, with about a third of patients achieving a complete response. Thus by the mid-1980s responses could be obtained in the majority of patients with SCLC, though relapse usually followed. It is upon this background that current attempts to improve the efficacy of the available chemotherapeutic agents are being made.

Use of alternating chemotherapy protocols

The strategy of using together two comparably effective chemotherapy regimens was widely tested in the 1980s,[15–19] a practice based in part on the work of Goldie and Coldman.[20] The majority of these studies compared CAV alone with CAV alternating with PE. In a Canadian trial an improved median survival was reported for the alternating CAV/PE regimen for extensive-stage patients.[15] However PE alone was not tested, so the apparent 'advantage' of alternating the two regimens was not rigorously demonstrated. No differences in median survival were noted in a Japanese study comparing CAV with CAV/PE and with PE alone.[16] Similar

Correspondence to Dr Malcolm Ranson
Senior Lecturer and Honorary Consultant in Medical Oncology,
CRC Department of Medical Oncology,
Christie Hospital NHS Trust, Wilmslow Road,
Manchester M20 9BX, UK
Tel: 0161 446 3000, Fax: 0161 446 3299

negative results were obtained by the Southeastern Cancer Study Group comparing CAV, the alternating CAV/PE, and PE alone. The respective overall response rates in this latter study were 58%, 58% and 59%, with respective median survivals of 38, 39 and 38 weeks.[17]

For patients with limited-stage disease, a cohort only studied in the Japanese trial, there was a survival advantage using the alternating regimen, but with the small number of patients in this subset this conclusion must be viewed with caution. The simple addition of etoposide to the CAV regimen may account for the improved survival in the Japanese trial, and not the use of an alternating regimen *per se*. This interpretation is supported by the results of a large SWOG study which found no survival advantage when comparing alternated CAV and PE with CAV plus etoposide (CAVE).[18] An earlier multicentre study also failed to reveal superior survival for patients treated with alternating CAV/PE compared to a regime of sequential CAV and PE.[19]

The conditions inherent in the use of truly non-cross resistant chemotherapy regimens embodied in the Goldie–Coldman hypothesis are not met by the CAV and PE regimens. Indeed the responses to 'crossover' chemotherapy seen in alternating CAV/PE chemotherapy trials indicate that CAV and PE are not truly non-cross resistant (Table 1). Overall, whilst there has been enthusiasm for the scientific rationale of alternating chemotherapy protocols in SCLC, this has not generally born fruit in practice.

Table 1. Response rates of patients who crossed over to second-line therapy following initial chemotherapy

Crossover		Reference
CAV to PE	PE to CAV	
9/39 (23%)	1/13 (8%)	16
13/59 (22%)	5/41 (12%)	17

Dose intensity in SCLC chemotherapy

The manipulation of dose intensity in the treatment of SCLC was first examined in a randomised trial of cyclophosphamide, methotrexate and CCNU[21] in which the cohort receiving the higher-dose regimen had superior complete response rate and median survival, and contained more long-term survivors. However, viewed in the context of modern chemotherapy, the arms of this trial would constitute a trial of low-dose vs very-low dose therapy. During the 1980s several small randomised studies were performed comparing modestly differing doses of CAV and these failed to show significant differences in clinical outcome between the regimens.[22] In a randomised trial in patients with extensive disease, Johnson *et al.*[23] compared 'high-dose CAV' to 'standard dose CAV'. The 'high-dose' arm consisted of cyclophosphamide 1.2 g/m^2, doxorubicin 70 mg/m^2 and vincristine 1 mg/m^2 every 3 weeks, whilst the 'standard' arm comprised cyclophosphamide 1 g/m^2, doxorubicin 40 mg/m^2 and vincristine 1 mg/m^2 every 3 weeks. The actual delivered dose intensity in the 'high-dose' arm was 27% greater than in the 'standard-dose' arm. The overall response rate and median survival for patients in the 'standard-dose' and 'high-dose' arms were not significantly different though the complete response rate was significantly superior for the more dose-intensive arm (22% vs 12%).

The impact of initial chemotherapy dose has also been investigated in a randomised trial in extensive-stage patients.[24] Patients randomised to the intensified arm in this study received increased doses of cisplatin and etoposide for the first two cycles, receiving standard doses in cycles 3 and 4. Though interpretation is complicated by the trial switching non-complete response patients to CAV therapy for cycles 5 to 8, there was no definable advantage for the group randomised to the early intensified therapy. The protocol increased the planned dose intensity by 67% though the increase in intensity achieved was rather less (46%). There was no excess in early deaths in this study but other investigators have observed that the risk of treatment-related death following the first cycle of chemotherapy is substantially higher than following subsequent cycles. This raises the possibility that attempts at early intensification may accentuate this early mortality risk for some patients.[25]

The possible importance of achieving early cytoreduction has also been examined in a French study.[26] In 105 patients using alternating radiotherapy/chemotherapy patients were randomized to receive a different dose of cisplatin (100 vs 80 mg/m^2 day 2) and cyclophosphamide (300 vs 225 mg/m^2 days 2–5) with identical doses of doxorubicin (40 mg/m^2 day 1) and etoposide (75 mg/m^2 days 1–3) for the first chemotherapy cycle. Thereafter, all patients received the same schedule for five further cycles using the lower cisplatin and cyclophosphamide doses. No significant differences in the total doses delivered after the first treatment were noted. The complete response rate was 67% in the higher-dose arm compared to 54% in the low-dose arm (p

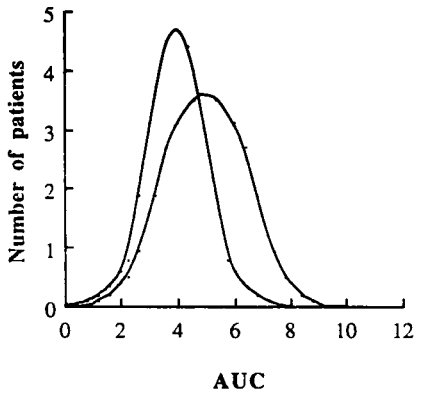

Figure 1. Distribution of patients' AUC for two doses of chemotherapy which differ by 25%. AUC distribution shown is typical of the 3- to 5-fold range of systemic exposure produced by dose normalisation to body surface area.

= 0.16). In spite of this non-significant difference in complete response rate, a significant survival advantage was observed for the high-dose group (52% vs 32% at 18 months).

As these examples illustrate, attempts to define dose–outcome relationships over limited ranges of dose intensity have not clearly confirmed a dose–response or dose–survival relationship in SCLC. Chemotherapy doses can be chosen which will diminish the response rate and shorten survival, but in seeking to identify whether modest dose intensification improves results many trials have been compromised by the small increase in dose intensity achieved, the small size of the studies, and the complexity of the relationship between dose intensity and measured outcome. In addition, it is now becoming more widely appreciated that traditional methods of cytotoxic drug dosing yield wide interpatient differences in systemic drug exposure, and this is likely to obscure the impact of modest changes in dose intensity.[27–29] *In vitro* dose–effect curves are often impressive, but *in vivo* interpatient differences of 3- to 5-fold in systemic exposure are encountered using body-surface area normalised dosing. For most cytotoxics, the area under the concentration–time curve (AUC) is the pharmacokinetic parameter that is most commonly correlated with pharmacodynamic variables (reviewed in ref. 29). Figure 1 illustrates a typical 3- to 5-fold variability in AUC using dose normalisation to body-surface area, and also the change in spectrum when the median AUC is increased by 25%. Furthermore, achieving a median increase of 25% in AUC usually requires a more substantial increase in surface-area normalised dose. For example, for doxorubicin a 100% increase in dose/m^2 will produce only a 46% increase in median AUC.[30] It is perhaps not surprising that defining dose–outcome relationships in clinical practice has proved so difficult within the confines of limited changes of dose intensity.

Use of weekly chemotherapy schedules

Non-randomised studies

One approach which offers the potential to increase dose intensity is to shorten the interval between chemotherapy cycles. In non-Hodgkin's lymphoma weekly regimens have been extensively investigated, making use of non-overlapping drug toxicities. Similar approaches have been explored in SCLC. Taylor treated 76 patients with a 16-week schedule of:

Weeks 1, 5, 9, 13 — doxorubicin 40 mg/m^2, cyclophosphamide 400 mg/m^2

Weeks 2, 6, 10, 14 — methotrexate 200 mg/m^2 + leucovorin rescue, vincristine 1.4 mg/m^2

Weeks 3, 7, 11, 15 — etoposide 75 mg/m^2/d × 3 days, cisplatin 60 mg/m^2

Weeks 4, 8, 12, 16 — vincristine 1.4 mg/m^2

In patients with limited-stage disease the response rate was 82% with a median survival of 16.6 months, whilst in patients with extensive disease the response rate was 81% with a median survival of 11.4 months.[31]

Other non-randomised weekly regimens extending over 9–12 weeks have been investigated[32–34] and have shown encouraging response rates (Table 2). Although these results appear quite promising they constitute non-randomised studies. Closer inspection suggests that patient selection factors may be influencing outcome. In the trial reported by Murray *et al.*, almost 50% of SCLC patients evaluated during the trial were excluded.[33]

Randomised trials

Encouraged by the results of a non-randomised, phase II trial of weekly chemotherapy with cisplatin, etoposide, ifosfamide and doxorubicin,[32] a follow-up, randomised trial was performed comparing this weekly regimen with a 3-week, alternating regimen using CAV and PE.[35] The 3-weekly and weekly regimens yielded almost identical results. Although the weekly regimen had a greater intended dose intensity, this was almost entirely offset by a greater incidence of dose reduction and delay in this arm. In the weekly chemotherapy group, 34.8%

Table 2. Trials of weekly chemotherapy in SCLC

Chemotherapy	Duration	No. of pts	Overall response (%)	Median survival	Reference
C, D, V, Et, P, M	16 weeks	34 L 42 E	82 81	17 months 11 months	31
P, Et, I, D	12 weeks	45 L 25 E	91 92	58 weeks 42 weeks	32
P, V, D, Et	9–12 weeks	48 E	94	61 weeks	33
P, V, D, Et + G-CSF	9 weeks	27 E	96	59 weeks	34
P, V, D, Et alone	9 weeks	26 E	85	35 weeks	
D, Et, P, Vd, V, M	18 weeks	44 L 54 E	84 57	58 weeks 39 weeks	37*
P, Et, I, D	12 weeks	141 L 80 E	82 84	11 months 10 months	35*

P = Cisplatin, C = cyclophosphamide, Et = etoposide, I = ifosfamide, D = doxorubicin, V = vincristine, Vd = vindesine, M = methotrexate, G-CSF = granulocyte-colony stimulating factor, L = limited disease, E = extensive disease. * Weekly regimen patients in randomised study.

of patients did not complete the intended programme, whilst 21.6% failed to complete the programme of the 3-weekly treatment. In a follow-on randomised study, the weekly regimen with granulocyte-colony stimulating factor (G-CSF) support was compared to weekly chemotherapy alone, but only a modest improvement in dose intensity (10%) could be achieved before other toxicities became dose limiting.[36] In 223 patients Sculier reported a randomised trial of weekly or 3-weekly chemotherapy.[37] Again the overall objective response rate was not significantly different between the two arms (69% in the weekly regimen, 61% in the 3-weekly regimen), but there was a significant response advantage for the weekly regimen in limited-stage patients. However, no significant differences in survival were seen, even on subgroup analysis.

A collaborative trial using cisplatin, vincristine, doxorubicin and etoposide is in progress, but the results of currently published randomised trials suggest that weekly regimens have limited scope for improving outcome in SCLC. A combined analysis of the randomised trials may be worthwhile to reveal if there is any further mileage in a weekly chemotherapy approach.

Use of haemopoietic growth factors to increase dose intensity

The application of recombinant DNA technology has resulted in the ability to identify, clone and produce a wide range of proteins for development as biopharmaceuticals. Myelosuppression is the commonest dose-limiting toxicity for cytotoxic drugs, and the clinical introduction of haemopoietic growth factors in the late 1980s offered exciting prospects for ameliorating or preventing some of the haemopoietic toxicity of cancer chemotherapy. Because G-CSF and granulocyte macrophage-colony stimulating factor (GM-CSF) are effective in accelerating myeloid recovery following chemotherapy, it is often possible to shorten the interval between chemotherapy cycles. Such 'accelerated' regimens typically result in greater increases in dose intensity than studies utilizing growth factors simply to supplement conventionally spaced treatment cycles to allow 'dose on time' therapy. The ability of G-CSF and GM-CSF to reduce the severity and duration of neutropenia induced by standard-dose chemotherapy has been well demonstrated,[38,39] but facilitating dose escalation must rank as being the most important attribute of the haemopoietic growth factors available.

It is important to realise that the widespread policy of dose reduction in addition to treatment delay for haemopoietic toxicity results in considerable reduction in dose intensity. A policy of allowing only dose delay but not additional dose reduction can be helpful in maintaining dose intensity.[40] One regimen with scope for dose intensification is ICE (ifosfamide, carboplatin and etoposide).[41–43] The dose-limiting toxicity of ICE and VICE (ICE and vincristine) regimens is primarily myelosuppression. Dose intensification with VICE has been investigated with or without GM-CSF.[44] Initial results

indicated that 3-weekly rather than 4-weekly treatment was possible in the majority of patients who received GM-CSF, and a median increase in dose intensity of 33% was achieved. In another study patients received VICE chemotherapy as soon as the blood count had re-constituted, and were randomised to receive or not receive G-CSF. There were no statistically significant differences in the incidence of febrile neutropenia, antibiotic use, days in hospital or transfusion requirements between the two groups. However, the 2-year survival was 15% for the non G-CSF compared to 32% for the G-CSF group.[45] Compared to standard 4-weekly VICE, the median increased dose intensity achieved by this approach was 25%.

Further dose escalation of ICE regimens is difficult because of thrombocytopenia. Several growth factors have thrombopoietic activity (GM-CSF, EPO, IL-3, IL-6, IL-1a), but as single agents their clinical thrombopoietic activity is often disappointing. Combinations of these cytokines and the thrombopoietic activities of others (stem cell factor, IL-11, IL-13, thrombopoietin) await investigation. Although we have a primitive understanding of the interplay of cytokines during normal haemopoiesis, there is ample evidence of powerful synergy for combinations of cytokines *in vitro* and in experimental animals. However, the clinical investigation of such synergistic combinations has been disappointingly slow.

Intensified chemotherapy using stem cell support

One of the most interesting ways to try to reduce the impact of marrow toxicity of chemotherapy and to facilitate increased dose intensity is to utilize peripheral blood progenitor cells. Evidence that haemopoietic progenitor cells existed in the peripheral blood of laboratory animals and humans was documented over 20 years ago.[46,47] Progenitor cells are mobilised from the bone marrow in significant numbers during normal recovery from myelosuppressive chemotherapy, and also by haemopoietic colony-stimulating factors such as G-CSF and GM-CSF when given to patients at steady state. Mobilisation of progenitor cells is markedly enhanced during colony-stimulating factor driven haemopoietic recovery after myelosuppressive chemotherapy. Whilst optimal schedules for the mobilisation of peripheral blood progenitor cells remain to be clarified, and depend upon treatment and patient cohort studied,[48–50] a single apheresis collection obtained during G-CSF or GM-CSF driven haemopoietic recovery can provide sufficient progenitor cells either for autografting after myeloablative therapy [48,51] or to be divided into aliquots and used to support multicyclic, sub-ablative treatments.[52–54]

The viability of haemopoietic progenitors in leukapheresis product and in venesected whole blood has been investigated.[53–55] The Manchester group have reported that the viability of harvested progenitors (assessed as granulocyte-macrophage colony forming units) was 67% in both whole blood or leukapheresis product stored in whole blood for 48 h at 4°C. This is equivalent to the viability after conventional cryopreservation and thawing. These data suggest that haemopoietic progenitors can be stored for limited periods at 4°C and used to support multicyclic chemotherapy. In a pilot study, untreated patients with good prognosis SCLC received six cycles of ICE chemotherapy with G-CSF and whole blood PBPC support. Ifosfamide at 5 g/m^2 iv over 24 h was administered on day 1 along with carboplatin 300 mg/m^2, and etoposide at 180 mg/m^2 on days 1 and 2. G-CSF was given at 300 μg subcutaneously on days 4–15. If white cell count was ≥ 3.0 × 10^9/L, platelets ≥ 30 × 10^9/L and creatinine clearance ≥ 60 ml/min, 750 ml of blood was taken by venesection and stored at 4°C for 48 h on day 15. These cells were reinfused 18 h after the last etoposide dose. By this approach, which did not require leukapheresis or cryopreservation, the dose intensity achieved was 100% greater than standard 4-weekly ICE.[53,54]

There is growing interest in the use of ex-vivo manipulation of progenitor cells with cocktails of haemopoietic growth factors such as IL-3, GM-CSF, G-CSF, stem cell factor and IL-6.[55–59] These approaches may further enhance the utility of progenitor cells in dose-intensive chemotherapy. Another novel approach to facilitate dose-intensive therapy may be to protect endogenous haemopoietic cells from chemotherapeutic cytotoxicity. Factors such as interleukin-1, macrophage inhibitory peptide 1α, leukocyte inhibitory factor and a number of short peptides are promising agents in this regard.[60]

Late intensification and myeloablative regimens

Late intensification as a strategy to improve outlook for patients with SCLC has been examined in highly selected cohorts of patients.[61–66] The vast majority of studies have been non-randomised. Not surprisingly, assessment of the impact of late intensification has proved very difficult since the attrition of patients before late intensification is administered is typically around 65% (Table 3). In a trial reported by

Table 3. Late intensification studies in SCLC

Stage	No. entering	No. receiving intensification	Chemotherapy	Median survival	Reference
L + E	36	14	C	10 months	61
L	32	12	C, Et, V	14 months	62
E	29	8	C, Et	5.5 months	63
L + E	101	45	C, Et, B	68 weeks	64
L	58	21	C	11 months	65

L = Limited disease, E = extensive disease, C = cyclophosphamide, Et = etoposide, V = vincristine, B = BCNU.

Humblet *et al.*[64] 101 patients received standard-dose CAV/PE chemotherapy and were then re-staged. Limited-stage patients with partial or complete responses and extensive-stage patients in complete response were randomized to further conventional-dose or high-dose intensification. The high-dose chemotherapy comprised cyclophosphamide, etoposide and BCNU and was followed by autologous bone marrow rescue. Of the initial 101, 45 patients were eligible for randomisation (39 with limited-stage disease) and their median relapse-free survival was 28 weeks vs only 10 weeks for the conventional-dose arm. Relapse-free survival in the conventional-dose arm was notably short, and the median survival of the two groups was not significantly different (68 vs 55 weeks).

There are a number of problems in the design of trials of late intensification and this may be partly because some have been designed as small-scale pilot studies. Thus, many of the studies included patients with extensive disease even though it is recognised that the cohort of patients most likely to benefit from late intensification are those with limited-stage disease who have minimal residual disease at the time of intensification. The doses of chemotherapy employed in some studies have not been significantly enhanced, and have sometimes not approached those routinely used in haematological malignancies. In addition a number of newer agents with potential for dose escalation (e.g. carboplatin) have not been adequately studied in late intensification. Until these issues are addressed it would be premature to conclude that late intensification has not been a successful strategy in SCLC.

Choice of drugs for dose escalation and their scheduling

In attempting to achieve dose escalation it is crucial that appropriate drugs are selected. One problem encountered with doxorubicin- and epirubicin-based regimens is that non-haemopoietic toxicity such as marked mucositis emerges at doses of doxorubicin > 100 mg/m^2 and troublesome skin toxicity is encountered at ≥ 125 mg/m^2.[30,67] Similarly, dose escalation of cisplatin is difficult to achieve because of the early emergence of nephrotoxicity and neurotoxicity.

Carboplatin

The cisplatin analogue carboplatin has significant activity in SCLC [68] and a more favorable toxicity profile.[69,70] Non-randomised studies have suggested that the two platinum analogues have comparable activity at conventional doses in SCLC.[12,71–74] A randomised phase III study of cisplatin/etoposide vs carboplatin/etoposide found that both combinations were equally effective but the carboplatin/etoposide arm was better tolerated, producing significantly less nausea, vomiting, nephrotoxicity and neurotoxicity.[75]

The use of carboplatin for dose escalation offers additional advantages other than an improved toxicity profile. The toxicity of carboplatin is more closely correlated with AUC than with dose per square metre body-surface area [76,77] and the renal clearance of carboplatin is close to the glomerular filtration rate over a wide range of renal function. Even though a small proportion of non-renal clearance occurs, the pretreatment renal function of a patient is therefore the main determinant of the systemic exposure, allowing AUC-targeted dosing to be employed. The impact of AUC on response in SCLC has not been addressed, but it is reasonable to assume that therapeutic effect may well be related to AUC by a Hill E_{max} model.

The Calvert formula [77] has been used in ovarian cancer to allow retrospective calculation of systemic exposure (AUC) for carboplatin, and the formula is increasingly used to guide dosing. There is

growing experience of carboplatin use in the context of very-high dose regimens with intensive haemopoietic support and it is in this setting that AUC-guided dosing may be particularly useful in standardising exposure.[78,79]

Etoposide

There is growing experience with escalated-dose etoposide in transplant conditioning regimens, but the use of etoposide in SCLC has been dominated by the observation of its schedule dependency in SCLC.[80,81] Early randomised studies suggested an advantage for oral dosing over 5 days rather than 3 days or 1 day in SCLC,[80] and a later small, randomised trial in extensive-stage SCLC patients demonstrated an improvement for five consecutive 2-h infusions of 100 mg/m^2, over a single 500 mg/m^2 24 h infusion.[81] Tumour response was significantly higher using daily dosing, with no difference in haematological toxicity. Although a comparison of plasma etoposide concentrations showed no significant differences for the two treatments in total AUC, half-life or volume of distribution, the time for which etoposide concentrations exceeded 1 μg/ml was significantly greater (94.5 h vs 46 h) with the 5-day regimen. Observations on the schedule dependence of etoposide have led to the prospective evaluation of more prolonged administration schedules in SCLC.[82–85] The development of prolonged administration regimens for etoposide has good molecular rationale in the dependence on cell cycle for topoisomerase II expression and the reversibility of the drug–enzyme–DNA complex. In addition, prolonged exposure may also be advantageous in overcoming drug resistance, as suggested by the promising results with EPOCH chemotherapy in relapsed and refractory non-Hodgkin's lymphoma.[86]

Etoposide shows highly variable pharmacokinetics between patients,[87–89] and systemic exposure and clearance are not correlated to body-surface area.[90,91] In the absence of measured or targeted plasma concentrations, administration can be simplified to a fixed dose independent of body-surface area. Though there appears to be a concentration threshold for the myelotoxic and therapeutic effects of etoposide, targeting a specific plasma level with oral etoposide is impracticable because of highly variable absorption of the drug, in addition to interpatient pharmacokinetic differences. Drug levels appear less variable with parenteral administration, and the use of measured drug levels to adaptively control administration may allow more precise definition of the therapeutic window.[91–93]

Cyclophosphamide and ifosfamide

The alkylating oxazaphosphorines ifosfamide and cyclophosphamide have been core drugs in many chemotherapy schedules for SCLC. Ifosfamide has been shown to have significant single-agent activity[94,95] and appears to be marginally less myelosuppressive than cyclophosphamide.[96] There are differences in non-haemopoietic toxicity between the two analogues at high dose: neurotoxicity may complicate high-dose ifosfamide therapy, whereas cyclophosphamide may have greater cardiotoxicity.[97–100]

Both cyclophosphamide and ifosfamide are prodrugs and require hepatic activation to yield their active metabolites.[101] The metabolism of cyclophosphamide and ifosfamide is complex and wide interpatient variation in their metabolic fate has been described.[102–104] Pharmacodynamic investigation has been hampered by considerable difficulties with assays of the parent drug and metabolites. Interestingly, with a 96-h infusion of high-dose cyclophosphamide as part of conditioning for autologous transplantation, Ayash reported that breast cancer patients with rapid rates of clearance of parent drug from the circulation were more likely to remain relapse-free, but also more likely to develop cardiotoxicity.[105]

There has been no formal investigation of the schedule dependency of cyclophosphamide and ifosfamide. However if the total dose is fractionated over several days, an increase in non-renal clearance is seen.[102] Repeated oral dosing or prolonged infusion of the drugs leads to similar changes in clearance.[106,107] These findings suggest that autoinduction of cytochrome P450 occurs with fractionation or prolonged administration. The impact of such differences in drug activation or handling on pharmacodynamic endpoints has not been addressed.

Conclusions

The concept of dose intensity has received considerable attention since the retrospective studies of Hryniuk in the 1980s in adjuvant and advanced breast cancer.[108,109] In addition to the well publicized limitations of retrospective dose-intensity analysis, closer inspection suggests that the conclusions drawn from such analyses are unduly influenced by dose intensities which fall below what would be considered standard dose in the 1990s. In the last seven years haemopoietic growth factors and peripheral blood progenitor cell support have

become widely used to increase the dose intensity of chemotherapy regimens. Their use may allow protocol dosing to be better maintained, or allow a modest (typically 30%–60%) increase in dose intensity. Using surface-area normalised dosing, interpatient differences in drug handling will yield a 3- to 5-fold interpatient range of systemic drug exposure,[29] and it is not surprising that clinical dose–response relationships can be difficult to ascertain. We must accept that we lack any comprehensive database on the shape of clinical dose–response/outcome curves and the recent trend towards dose-intensive regimens has simply served to emphasize the paucity of information we have on the pharmacodynamics of anticancer drugs. Attempts to define these relationships prospectively over limited ranges of dose intensity are compromised by the complexities of the relationship between dose and measured outcome. Over the last few years we have perhaps become beguiled by the technology of stem cell harvesting and haemopoietic growth factors, yet none of this therapeutic advance can be optimised unless we also devote attention to improving the effectiveness and tolerability of our treatment regimens. The lack of clear understanding of the pharmacodynamics of anticancer drug action has compromised our ability to rationally improve therapeutic efficacy. In addition, there are deficiencies in current dosing strategies based upon normalisation to body-surface area, and attempts to improve dosing strategies are worthy of investigation.

Sequential studies of the treatment of patients with limited-stage SCLC have demonstrated its potential curability. Whilst there may be some bias introduced by high technology staging resulting in the 'Will Rogers' phenomenon and stage-shifting of patients,[110,111] both the median duration of survival and the number of long-term survivors for comparably staged patients appears to be slowly improving.[39] For patients with SCLC there remains a pressing need for the development of new and effective agents. Whilst there may be gains for patients with more favourable prognostic factors by applying dose intensification, for patients with poor prognostic factors dose escalation frequently produces little definable positive impact on survival or quality of life. Nevertheless, as the experience with etoposide and infusional approaches[112] has demonstrated, there can sometimes be potential in attempting to define optimal drug scheduling.

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