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# First-line chemotherapy rechallenge after relapse in small cell lung cancer

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**Summary.** Response to second-line therapy in relapsing patients with small cell lung carcinoma (SCLC) is often claimed to be evidence in favour of non-cross resistance. Fifteen patients with SCLC who had relapsed off treatment after responding to initial first-line chemotherapy were retreated with the same regimen at relapse. Ten (67%) achieved a further partial response. Median response duration was only 3 months (range 2–4 months), but similar poor results have been reported for most studies using second-line chemotherapy. Relapse in SCLC does not necessarily imply complete clinical resistance to first-line chemotherapy, and strict clinical criteria are required to demonstrate true non-cross resistance

## Introduction

Despite a high initial response rate to chemotherapy, SCLC relapses in most patients within a year of starting treatment. This failure is usually ascribed to specific drug resistance, and relapsing patients are often offered alternative, second-line chemotherapy. This approach is based on the exploitation of so-called non-cross resistance with the first-line combination [4] and assumes that resistance to the original drugs is such that responses will not be obtained by rechallenge with them [12].

This concept is so widely accepted that references in the literature to same drug rechallenge are few [2]; more commonly, they refer to individual drugs repeated as part of different combinations [16] or given as single agents [8]. The efficacy of rechallenge chemotherapy has, however, been documented in Hodgkin's disease [6] and breast cancer [3, 19]. To investigate whether complete drug resistance really does develop in SCLC, we rechallenged relapsed patients with their identical first-line chemotherapy.

## Patients and methods

Fifteen patients were referred to the Lung Unit, Royal Marsden Hospital, sutton, with histologically proven SCLC. They had relapsed off treatment after responding to initial first-line chemotherapy and were retreated with the same chemotherapy regimen at relapse. Their median age at presentation was 63 years (range 57–73 years) and 13 were male. At initial presentation, 8 had had limited disease (LD) and 7 extensive disease (ED). At the time of rechallenge chemotherapy after relapse, only 2 still had LD and 13 had ED. At rechallenge, 3 patients had an ECOG performance status (PS) of 1; 7 were PS 2; 5 were PS 3.

All patients received their initial chemotherapy at our unit between march 1982 and October 1985 according to protocols then current. Ten patients received a combination of carboplatin (300 mg/m$^2$ × 1 day) and etoposide (100 mg/m$^2$ × 3 days) at 4-week intervals for four cycles. Three patients received a combination of doxorubicin (Adriamycin; 40 mg/m$^2$ × 1 day), etoposide (100 mg/m$^2$ × 3 days), and vincristine (1.4 mg/m$^2$ × 1 day; maximum 2 mg) at 3-week intervals for four cycles, with subsequent high-dose cyclophosphamide (7 g/m$^2$) for two cycles. Two patients received monthly carboplatin alone (1 at 400 mg/m$^2$ for 5 cycles, the other at 800 mg/m$^2$ for 2 cycles). Nine patients achieved a partial remission (PR) and 6 a complete remission (CR) with their induction chemotherapy.

All patients were rechallenged at relapse with the same drugs and scheduling, although 7 patients had 25%–50% dose reductions because of toxicity. In 11 patients, rechallenge chemotherapy was given at first relapse; in the other 4, radiotherapy and/or alternative chemotherapy was administered at first relapse and rechallenge chemotherapy was administered at second relapse. One patient (no. 7) was successfully rechallenged on two occasions. Details of the patients' response criteria, their treatments, and clinical course are given in Table 1.

## Results

The median number of rechallenge chemotherapy cycles received was three (range 1–5). In all cases treatment was stopped because of disease progression rather than toxicity; treatment rarely had to be deferred.

Ten patients achieved a PR to rechallenge chemotherapy (67%), including one on two separate occasions; no patient achieved a CR. Four patients experienced rapid disease progression and one, who was treated with another drug 2 weeks after the first rechallenge, is not assessable. Six of the ten JM8/VP16 patients achieved PR, three developed PD and one was not assessable; two of the three adriamycin/VP16/vincristine patients responded and both patients responded who were retreated with the single agent JM8.

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**Table 1.** Response eriteria, treatment, and clinical course

| | Presentation age, sex, and extent of disease | Initial chemotherapy | Response and duration (months) | Treatment of first relapse and response and duration (months) | Rechallenge chemotherapy | Performance status and disease extent at rechallenge | Response to rechallenge and duration | Survival after rechallenge and cause of death | Final outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1. | 56 M ED | JM8/VP16 ×4 | PR; 6 | RT; PR; 4 | JM8/VP16 ×1 | 3 ED | PD | <1 PD | Died 11 days after first rechallenge |
| 2. | 58 M ED | JM8/VP16 ×4 | CR; 5 | Rechallenge | JM8/VP16 ×1 | 2 ED | Not assessable | 4 PD | Ifos given 2 weeks after 1st rechallenge; transient PR then dies |
| 3. | 66 M LD | JM8/VP16 ×4 | CR; 6 | Rechallenge | JM8/VP16 ×1 | 1 LD | PD | 1 PD | |
| 4. | 69 M LD | JM8 400 mg/m² ×5 | PR; 11 | Rechallenge | JM8 400 mg/m² ×5 | 2 LD | PR; 3 | 8 PD | Fails CMV after rechallenge |
| 5. | 56 M LD | Adr/VP16/ Vcr ×4; HDC | PR; 20 | Rechallenge | Adr/VP16/ Vcr ×2 | 2 ED | PD | 3 PD | |
| 6. | 60 M | Adr/VP16/ Vcr ×4 | CR; 4 | JM8; NC; 6 ×6 | Adr/VP16/ Vcr ×2 | 3 ED | PR; 2 | 5 PD | |
| 7. | 69 M LD | Adr/VP16/ Vcr ×4; HDC | CR; 30 | Rechallenge no. 1; Rechallenge no. 2 | Adr/VP16/ Vcr ×3<br>Adr/VP16/ Vcr ×2 | 1 ED<br>3 ED | PR; 3<br>PR; 1 | 22<br>3 PD | RT controls disease until further relapse necessitates a 2nd rechallenge |
| 8. | 61 M | JM8/VP16 ×4 | CR; 5 | Rechallenge | JM8/VP16 ×4 | 3 ED | PR; 2 | 3 PD | |
| 9. | 73 M LD | JM8/VP16 ×4 | PR; 5 | Rechallenge | JM8/VP16 ×1 | 2 ED | PD | <1 PD | Dies 10 days after rechallenge |
| 10. | 57 M ED | JM8/VP16 ×4 | PR; 13 | Rechallenge | JM8/VP16 ×3 | 2 ED | PR; 2 | 4 PD | No benefit from further CMV |
| 11. | 69 F ED | JM8/VP16 ×4 | PR; 4 | RT; CMV ×4; PR; 4 | JM8/VP16 ×2 | 2 ED | PR; 2 | 3 PD | No benefit from further VAC |
| 12. | 51 F LD | JM8 800 mg/m² ×2 | PR; 3 | Rechallenge | JM8 400 mg/m² ×2 | 3 ED | PR; 2 | 3 PD | |
| 13. | 60 M ED | JM8/VP16 ×4 | CR; 7 | Rechallenge | JM8/VP16 ×4 | 1 ED | PR; 2 | 6 PD | |
| 14. | 69 M ED | JM8/VP16 ×4 | PR; 10 | RT; PR; 5 | JM8/VP16 ×5 | 1 ED | PR; 4 | 4 PD | |
| 15. | 64 M LD | JM8/VP16 ×4 | PR; 12 | Rechallenge | JM8/VP16 ×5 | 2 ED | PR; 3 | 5 PD | |

*Abbreviations:* JM8, Carboplatin; VP16, etoposide; C, cyclophosphamide; HDC, high-dose cyclophosphamide; Adr, Adriamycin; Vcr, vincristine; M, methotrexate; Ifos, ifosfamide; RT, radiotherapy; LD, limited disease; ED, extensive disease; M, male; F, female; PR, partial remission; CR, complete remission; NC, no change; PD, progressive disease

The overall median response duration was 3 months (range 2–4 months). Of the six JM8/VP16 responses, three lasted 2 months, two lasted 3 months, and one lasted 4 months. Of the two responses in the adriamycin/VP16/vincristine group, one lasted 2 months and the other lasted 3 months. The two single-agent JM8 responses lasted 2 and 3 months, respectively. The median survival of the ten responding patients was only 5 months from the start of rechallenge chemotherapy, although one survived 25 months (range 3–25 months). The median survival of the 5 non-responding patients was only 1 month (range <1–3 months).

The likelihood or duration of a second response was not influenced by the extent of the response (CR or PR) to the first session of chemotherapy. However, the duration of the first response did influence the likelihood of a relatively durable second response on rechallenge (Table 2); first responses of longer than 8 months were more likely to

**Table 2.** Likelihood of a good second response is a function of duration of first response ($P = 0.02$)

| First response | <8 months | >8 months |
|---|---|---|
| NR or second response <2 months, or NR | 8 | 1 |
| Second response >2 months | 1 | 4 |

be associated with a second response of more than 2 months ($P = 0.02$; Fisher's exact test).

## Discussion

This study demonstrates that it is possible to achieve a high proportion of responses by rechallenging relapsed SCLC patients with the same treatment that was initially effective. These responses were neither complete nor enduring, but this is usually also true for "non-cross resistant" second-line chemotherapy (see below), and our results conflict with the dogma that second-line chemotherapy has to be both different and non-cross-resistant to be effective in this context. Similar findings have been published by Batist et al. [1], although their patients all had prolonged (>2 year) complete remissions before reinduction with the same chemotherapy.

Response to rechallenge chemotherapy suggests that our first-line therapy may not have been of adequate duration, and four courses of treatment is certainly less than most conventional regimens. However, our median survival for all patients treated on these regimens was around 12 months for patients with limited disease and 7 months for those with extensive disease [17, 18]; these results are similar to those reported from most other large studies using more protracted chemotherapy [7, 14].

Despite the inadequacy of rechallenge chemotherapy in our patients, the responses achieved in each case were symptomatically worthwhile. Comparison of our results with the standard approach in relapsed SCLC is complicated by the inclusion of primary treatment failures in the literature. However, we have identified seven studies (192 patients altogether) employing so-called non-cross-resistant chemotherapy in clearly distinguishable relapsed patients [2, 5, 9–11, 13, 15]. These studies are listed in Table 3, with our patients for comparison. Their response rates (CR + PR) for these studies range from 6% to 31%, and the median survival of responding patients was usually only 3–4 months. Thus, results with rechallenge chemotherapy, although poor, appear to be no worse than with alternative second-line chemotherapy.

Given the probability that rechallenge chemotherapy is not less effective than standard alternative second-line

**Table 3.** Published data using "non-cross-resistant" chemotherapy on SCLC relapses compared with this study

| Authors | Patient number | First treatment | Second treatment | CR + PR (%) | CR (%) | PR (%) | MR/SD (%) | Duration |
|---|---|---|---|---|---|---|---|---|
| Batist et al. [2] | 18 | C, M, Cc Pro, Adr, Vcr VP16? | VP16/Plat | 11 | 0 | 11 | 6 | 2 PRs last 3.5 and 4 mths; 1 MR last 2 mths; 1 SD last 5 mths. Others "progress or die" in 3 mths |
| Joss et al. [2] | 18 | ? | Vds, Hex | 6 | 0 | 6 | 11 | 1 PR last 3.5 mths; 2 SD for 4 and 5 mths |
| Niederle et al. [13] | 32 | Adr, C, Vcr Cc, VP, M, Ifos | Vds, Plat | 19 | 6 | 13 | 32 | 2 CRs survive 9.5 and 15 mths. Median survival "less than CR" 3 mths |
| Joss et al. [12] | 13 | ? | Mito, Hex, Vds | 8 | 0 | 8 | 46 | 1 PR and 6 SD survive at 3.5 mths. 6 PD survive at 3 mths |
| Poplin et al. [15] | 29 | Adr, C, VP16 | Cc, Vcr, M Pro | 31 | 17 | 14 | ? | Median survey. CRs 11 mths. Median survey. PRs 3 mths |
| Evans et al. [5] | 18 | C, A, V or C, M, V | VP16 | 6 | 0 | 6 | – | 10 weeks, then Plat added |
| Evans et al. [5] | 34 | C, A, V or C, M, V | VP16/Plat | 44 | 0 | 44 | 32 | Median survival 29 weeks for PRs |
| Lopez et al. [11] | 30 | C, A, V or Pro, V, C, CCNU or M, A, C, CCNU | VP16/Plat | 27 | 7 | 20 | | Median survival 12 mths for CRs, 6 mths for PRs |
| This study | 15 | JM8, VP16 | Identical | 67 | 0 | 67 | 0 | Median response for 3 mths. Median survey resp. 4.5 mths; non-resp. 1 mth |

*Abbreviations:* See Table 1. Hex, Hexamethylmelamine; Vds, vindesine; Plat, cisplatin; Cc, CCNU; Mito, mitomycin-C; Pro, procarbazine; Ifos, ifosfamide; MR, minor response; SD, stable disease; Resp, responders; mths, months

treatment in salvage, it is possible that the efficacy of apparently non-cross-resistant chemotherapy is accounted for by the same high proportion of drug-sensitive cells identified by rechallenge chemotherapy. The patent inadequacy of both approaches supports this contention, implying as it does that at relapse, there exists an initially low but crucial proportion of cells resistant to any available type of chemotherapy.

Our results do not argue against the concept of non-cross-resistance, but they suggest that claims to support the concept based on second-line chemotherapy response for patients relapsing off first-line treatment [2, 9, 10, 13, 15] may be invalid. Non-cross-resistance in a clinical context depends on the demonstration of response to second-line chemotherapy in a tumour that is clearly progressing on first-line treatment.

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