21%, docetaxel 75 mg/m^2 群で32%, vinorelbine もしくは ifosfamide 群で19%と docetaxel 75 mg/m^2 で良好であった.

これらの臨床試験の結果, 欧米ではプラチナ製剤によるファーストライン治療後の再発例には docetaxel 75 mg/m^2 の単剤使用が標準的と考えられている.

2 Pemetrexed

Pemetrexed (Alimta) は葉酸と似た構造式を持ち, 葉酸などの代謝拮抗剤としてがん細胞の増殖を抑えるというものである. さらに総合ビタミン剤, ビタミンB12の併用により血液毒性を軽減させることができるため, 臨床試験では1,000 mg/m^2 までの投与が実施されている. Pemetrexed はセカンドライン治療として使用した場合, docetaxel と比較して奏効率, 生存期間ともにほぼ同じであることが海外の第Ⅲ相臨床試験で判明しているが, Pemetrexed の大きな特徴は docetaxel よりも毒性が軽いことである[35]. 今後 docetaxel に加えてセカンドライン以降の治療の中枢をなす薬剤となることが期待される (表5).

おわりに

近年, 化学療法の研究が従来の抗がん剤からいわゆる分子標的薬にシフトしていることは明らかであるが, 従来の抗がん剤を用いてさらに治療成績を向上させることを期待して, sequential chemotherapy のランダム化第Ⅱ相試験 (SWOG9806) が実施された. Sequential chemotherapy は Norton-Simon の理論などに基づいて, 1つの化学療法を最大効果があがるまで繰り返した後に, 次の化学療法レジメンに切り替える方法である. SWOG9806 では, carboplatin+gemcitabine 3コース投与後に paclitaxel 3コースを投与する方法と cisplatin+vinorelbine 3コース投与後に docetaxel 3コースを投与する方法が検討された. しかし, いずれの方法でも生存期間中央値は9カ月であり, 第Ⅲ相試験に進めるような結果は得られなかった. 既存の抗がん剤を用いて治療成績を向上させる試みとして, sequential chemotherapy 以外にも3剤併用, プラチナ製剤を含まない併用化学療法などが行われてはいるが, いずれも既存の成績を凌駕するものではない.

今後は, gefitinib (Iressa) などの分子標的薬をいかに有効に既存の抗がん剤と併用するかが重要な課題と考えられる. また, 血管新生阻害作用を有するモノクローナル抗体である Bevacizumab など, 肺がんに対しても効果が期待される EGFR 以外を標的とした分子標的薬の開発にも期待が寄せられている.

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特集 増え続ける肺癌－治療成績を向上させるために

肺小細胞がんに対する治療法とその選択

Treatment selection of small-cell lung cancer (SCLC)

野田 和正
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肺小細胞がんの治療は1970年代以降徐々に改善され，State of The Artも2002年に改定され，予後良好群が確立されている．切除が可能な例は少なく，I・II期例が対象であり，術後の化学療法の追加が必要である．ほとんどの症例は切除不能であり，限局型には化学療法と放射線療法の併用が，進展型には化学療法単独が行われる．

肺小細胞がんの診断は，気管支鏡下の病巣生検の組織診・細胞診，末梢病巣擦過・洗浄・生検，あるいは経気管支鏡的縦隔リンパ節穿刺による細胞診・組織診により下されるが，生検材料ではしばしば組織が坐滅してしまい組織診が困難なことがあり，細胞診が助けとなることがしばしばある．また腫瘍マーカーでPro GRPやNSEが高値である場合は肺小細胞がんである可能性が考えられるが，非小細胞がんでも低分化型ではしばしば上昇するので補助診断にはなりにくい．ただし，肺小細胞がんが確定している場合にはこれらの腫瘍マーカーが高値であれば，その後の治療効果の目安に使うことができる．

肺小細胞がんの診断が確定すると，肺非小細胞がんと同様に病期分類を行い，それに基づいて治療方針を決定することになる．肺小細胞がんではたいていの場合は縦隔・肺門リンパ節転移や遠隔転移を伴っていることがほとんどであり，手術の適応となる場合は少ない．しかし，I期例は数少ないが手術対象となる．

肺小細胞がんの治療は1970年代以降徐々に改善され[1]，1981年に公表されたState of The Artも2002年に改定され[2]，予後良好群が確立された．しかし，ここでは切除可能例と切除不能例(限局型例，進展型例)に分けて考えることとする．

I. 切除可能例

肺小細胞がん限局例の中でもI期，とくにc-T1N0M0例については手術療法単独や[3][4]，手術に化学療法を併用することにより，5年生存率は40～70%と報告されている[3]-[5]．しかしこのような症例は対象例数も少ないために比較試験もないが，対象例数30例以上を集積した報告で見ると，手術単独よりは化学療法を併用する方が予後の改善効果がある[5]．術後の放射線治療については報告がない．

実地臨床においては，術前には確診がつかず，

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Key words：肺小細胞がん 化学療法 限局型 進展型

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切除して始めて小細胞がんと診断される症例も多く，外科切除後に化学療法を施行することは有用である。

以上より，術前にしろ術後にしろI期の肺小細胞がんと診断がついた場合には，術後に化学療法を施行する必要がある。肺小細胞がんはリンパ節転移や遠隔転移をきたしやすいがん腫であり，郭清できたから化学療法を施行しないということはすすめられない。この場合に選択される化学療法レジメンとしては切除不能例における場合と同様に，シスプラチン＋エトポシド(PE)療法であり，これを2コース以上施行する必要がある。シクロフォスファミド＋ドキソルビシン＋ビンクリスチン(CAV)療法やカルボプラチン＋エトポシド療法についても，残存しているがん細胞の量は非常に少ないと考えられるので，有効であると考えられる。

II. 切除不能例

多くの肺小細胞がん症例では，縦隔リンパ節転移(N2以上)あるいは遠隔転移(M1)を伴っており，臨床病期分類ではIIIA期以上である。肺小細胞がんは化学療法とも放射線療法のどちらの治療法にも感受性が高く，治療としては限局型では化学療法＋放射線療法が行われ，進展型では化学療法単独の治療が行われることになる。とくに限局型では放射線療法の併用により治癒も望むことができる。進展型では化学療法単独となるので，治癒を望むことはむずかしい。限局型と進展型を分ける境界は，放射線照射を併用施行できるかどうかである。胸部・上腹部CT，脳MRI(CT)，骨シンチ(またはPET)により，進展範囲を把握する必要がある。限局型であれば骨髄穿刺を施行して骨髄浸潤がないことを確認しておく必要がある。すでに知られていることではあるが，TNM分類は肺非小細胞がんやI・II期の肺小細胞がんのような手術対象例においては切除術式の決定には重要なものであるが，進行例が多く，したがって化学療法や放射線療法が治療の主体となる肺小細胞がんの多くでは，放射線照射の併用の可否を決定することが先決であり，このような場合にはTNM分類のような詳細な分類よりも，限局型か進展型かの決定でも十分である。

III. 限 局 型

限局型の肺小細胞がんにおいては，化学療法と胸部放射線療法の併用に関するメタアナリシスの結果，化学療法単独よりも併用のほうが生存を改善することが明らかにされた[6][7]。また3つの臨床試験において胸部放射線療法と化学療法を早期に同時併用することにより生存が有為に改善することが示された[8)-10)]。これらの比較試験では，ほとんどの場合で化学療法はシスプラチン＋エトポシドの併用療法(PE)が用いられており，施行コース数は4コースである。照射は1回2 Gyを1日1回で総線量45 Gyが標準である。

化学療法と胸部放射線療法を併用する場合に，通常照射法(1.8 Gy/回/日，5週)と多分割照射法(1.5 Gy/回×2回/日，3週)との比較試験が行われ[11]，加速多分割照射法が通常照射法に比べて予後の改善が大きいことから，施設の放射線治療能力に余裕がある場合は1日2回法を行う加速多分割照射法を施行することが望ましい。

イリノテカン＋シスプラチン(IP)療法は進展型の肺小細胞がんに対する臨床試験においてPE療法より予後の改善が有意によかったという結果から[12]，放射線療法とIP療法を併用することが当初考えられた。しかし，イリノテカンと放射線の併用により肺障害の出現のリスクが大きいので[13]，放射線照射との併用は避けたほうがよいと考えられる。これらの経験から，JCOGでは現在進行中の限局型の肺小細胞がんに対する臨床試験では，1コース目の化学療法はPE療法を行うと同時に胸部照射を加速多分割法で行い，2～4コース目をPE療法かIP療法かで無作為化割付する比較試験を行っている。

高齢者やPS不良例ではカルボプラチン＋エトポシド療法も有用であり，進展型ではシスプラチ

ン＋エトポシドとほぼ同等であることが報告されているが[14]，限局型ではエビデンスが少ないものの，放射線照射との併用は可能である．しかし，このような症例に対しては，同時併用よりも化学療法を先行させ，その後に放射線照射を追加する異時併用の方が安全である．

また，胸部放射線照射の範囲が一側肺の半分を超える場合は，放射線療法による障害のリスクが増加するので，治療計画を立てる際にはその点に注意を払う必要がある．化学療法との併用に際しては照射範囲の拡大は避けるべきであり，このような場合にも化学療法を先行して，腫瘍が縮小したのちに放射線照射を追加する方がリスクは少ない．

胸水貯留は放射線照射の適応ではなく化学療法主体となるので，進展型として扱う．

IV. 進 展 型

これまで行われてきた肺小細胞がんに対する臨床試験は75歳未満，PS 0-2 の患者が対象となっており，これらの症例に対して化学療法を行うことに問題はなく，PS 不良例(PS 2-3,) や高齢者に対しても至適な化学療法を検討する臨床試験が行われており[14]，有意であったかどうかは別として，PS 不良や高齢であっても化学療法を行う意義がある．しかし，PS 4 の患者に対して化学療法に関するエビデンスはない．

1970年代にはシクロフォスファミドを中心とした多剤併用療法が多数検討され，その中でシクロフォスファミド＋ドキソルビシン＋ビンクリスチンの 3 剤併用(CAV)療法が標準的治療法として確立された[15]．その後，エトポシドとシスプラチンが登場し，CAV 療法におけるエトポシドの組み込みやシスプラチン＋エトポシドの併用療法が1980年後半から1990年代初頭にかけて検討されたが，CAV 療法との比較で生存期間の有意な差は認めず[16][17]，CAV 療法と PE 療法はほぼ同等と考えられた．また，CAV/PE 交替療法と CAV 療法との比較試験[16]-[18] のうちのひとつで[18]進展型症例において交替療法群での生存が有意に延長したことから，これらと CAV/PE 交替療法の治療成績はほぼ同等と考えられた．

しかし，CAV 療法後の再発例に対する PE 療法では奏効率が40～50%であったのに対して，PE 療法後の CAV 療法では奏効率15%以下であったこと[16]-[18]，PE 療法は 4 サイクルが標準であるのに対して，CAV 療法と CAV/PE 交替療法は 6 サイクル施行を要することから，PE 療法がより有用であり，しかも短期間で終了でき，煩雑でないことなどのため，PE 療法が最も頻用されてきた．

小細胞肺がんの治療にシスプラチンが必要かどうかを検討したメタアナリシスにおいては，シスプラチンを含むレジメンがシスプラチンを含まないレジメンより，治療関連死を増大させることなく，奏効率，6 ヵ月生存率，1 年生存率の有意な改善が認められたとしている[19]．

シスプラチンとエトポシドにさらに別の薬剤を加えることの有用性は明確ではない．

1990年代に出現したイリノテカンについて，JCOG 試験で PE 療法 vs イリノテカン＋シスプラチン(IP)療法の第 III 相試験が行われ，IP 療法が PE 療法に比べ有意に生存期間が延長することが示された(生存期間中央値 12.8 vs 9.4ヵ月)[12]．この併用療法については米国で二つの追試が行われており，そのうちのひとつで生存に有意差がなかったことが2005年の ASCO 総会で発表された[20]．しかし，この試験ではシスプラチンを分割投与していることと，イリノテカンが 1 コースで 2 回しか投与されていなかったことにより，JCOG 試験の結果と異なって，生存に差が出なかったのではないかと考えられる．なお，イリノテカンでは下痢が特徴的な毒性として挙げられるが，JCOG 試験では[12] IP 群77例中の 3 例において著明な下痢を含む治療関連死を認めており，また Grade 3/4 の下痢も多かった．これらを含めた grade 3 以上の非血液毒性は，1・2 コース目に生じていることから，イリノテカンの投与時の患者の臨床症状には注意を払う必要があり，とくに

治療開始1・2コース目においては十分に患者の全身状態を把握することが肝要であり，イリノテカン投与予定日に少しでも下痢の兆しがある例でイリノテカンの投与は避ける(スキップ)べきである．またGrade 3以上の毒性出現に際してはそれが十分に回復可能と推測される症例を対象と考えるべきであり，PS良好例をその治療対象とする．骨髄毒性については，PE療法のほうがIP療法よりも強く[12]，米国での臨床試験においても同様の結果が報告されており[20]，骨髄毒性出現に際してはG-CSF投与など早急に対処する必要がある．

カルボプラチン＋エトポシドの併用療法とシスプラチン＋エトポシド(PE)療法の比較試験では両群間で生存期間に有意な差は認めなかった[21]．しかし，カルボプラチン＋エトポシドは，シスプラチン併用レジメンにおける場合のような大量の輸液を必要としないこともあり，高齢者を対象とした場合には有用であると考えられる．JCOGでは70歳以上の高齢者に対してシスプラチン＋エトポシド併用とカルボプラチン＋エトポシド併用の比較試験が行われ，その結果が2005年のASCO総会で発表されたが，両群間で生存に差が見られなかった[14]．カルボプラチン＋エトポシドはシスプラチン併用レジメンと異なって大量輸液を必要とせず，消化器毒性も軽度であるので，高齢者やPS不良例においては考慮すべきレジメンである．また外来通院での施行も可能であり，今後の日本の実地医療に寄与するものと考えられる．しかし，血小板数減少は強いので[14]，外来通院に際しては血液検査による経過観察はとくに重要である．

胸水貯留が大量の場合にはイリノテカンの使用は禁忌であり，またシスプラチン＋エトポシド併用療法は腎障害予防のための大量の輸液負荷が必要となるので，心機能への負担が大きくなるリスクもあり，施行不可能と考えられる．このような場合にはシスプラチンをカルボプラチンに変更することでリスクを減らすことができる．なお，胸水のコントロールが成功している場合にはイリノテカンの使用は可能であり，また大量の輸液負荷にも耐えられると考えられ，イリノテカン＋シスプラチン療法の施行は可能である．

おわりに

肺小細胞がんにおける化学療法の進歩は世界的にも目覚しいものがあり，その中で日本発のエビデンスが重要な位置を占めている．今後，アムルビシンやノギテカンに関する知見も判明してくるものと考えられるが，これらについてはまだ比較試験が行われていない現状であり，今後の発展を期待したいところである．

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Phase II Study of Weekly Paclitaxel for Relapsed and Refractory Small Cell Lung Cancer

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Abstract. *The purpose of this study was to evaluate the efficacy and toxicity of single-agent paclitaxel given weekly to patients with relapsed and refractory small cell lung cancer (SCLC). Patients were treated with 80 mg/m^2 paclitaxel administered weekly for 1 h for 6 weeks in an 8-week cycle. Twenty-two patients were enrolled, 21 of whom were eligible. The patient characteristics included: 20 males, 1 female; median age 66 years (range 48 - 75); performance status 0/1 in 19 and 2 in 5 patients. Grade 3/4 leukopenia and neutropenia occurred in 47.5% and 64%, respectively. Other grade 3/4 toxicities included infection, skin rash, neuropathy and pulmonary toxicity. There were 5 partial responses in 3 out of the 11 sensitive cases and 2 out of the 10 refractory cases, respectively. Paclitaxel, administered as a weekly infusion at a dose of 80 mg/m^2, was effective in treating relapsed and refractory SCLC.*

More than 95% of patients with small cell lung cancer (SCLC), who are initially treated with paclitaxel 80 mg/m^2, present a relapse and their response to a second-line therapy is poor. The responses obtained are usually brief, and the median survival is generally less than 4 months (1). Nevertheless, second-line chemotherapy may provide a significant palliation of symptoms and does result in a prolongation of survival in many patients.

The activity of paclitaxel as a single agent has been investigated in both previously-untreated and -treated SCLC patients. Two phase II trials were conducted to investigate its efficacy as a first-line treatment for SCLC. In a trial conducted by the Eastern Cooperative Oncology Group (ECOG), Ettinger *et al.* administered 250 mg/m^2 paclitaxel as a 24-h infusion to 36 patients (2), among whom 11 partial responses were observed. Kirschling *et al.* obtained a similar response rate, 41%, in a group of 37 patients on an identical paclitaxel dose-schedule (3). The results of a phase II study in previously treated patients were reported by Smit *et al.* (4). All 24 patients in that trial developed progressive disease within 3 months of receiving at least one previous chemotherapy regimen. Seven patients (29%) had a partial response to 175 mg/m^2 paclitaxel as a 3-h infusion. These data show that paclitaxel exhibits single-agent efficacy in SCLC comparable to that of the best agents. The results of Smit *et al.'s* study in patients with refractory SCLC are particularly impressive, since most response rates reported with single-agent or combination regimens in this population have been less than 15%. However, life-threatening toxicity occurred in 4 of these patients, 2 of whom experienced hematological toxicity.

Recent reports of the activity and tolerability of weekly doses of paclitaxel have generated a great deal of clinical interest. Weekly paclitaxel therapy has generally been quite well tolerated, causing minimal toxicity and no apparent cumulative myelosuppression. Substantial evidence from clinical trials indicates that weekly paclitaxel is effective and generally well tolerated as both a first- and second-line treatment for advanced NSCLC. A phase I/II trial by Koumakis *et al.* in a second-line setting tested weekly paclitaxel infused for the first 6 weeks of each 8-week cycle,. and demonstrated that a paclitaxel dose escalation from 60 mg/m^2 to 90 mg/m^2 was tolerated (5).

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Fennelly *et al.* reported a recommended dose of 80 mg/m^2 administered weekly for 6 weeks of an 8-week cycle in patients with recurrent ovarian cancer (6).

Based on this evidence, a phase II trial of 80 mg/m^2 weekly paclitaxel as a 1-h infusion for 6 consecutive weeks followed by 2 weeks without treatment (8-week cycle) was conducted in patients with relapsed SCLC. The objective of this study was to evaluate the efficacy and safety of weekly paclitaxel in patients with relapsed and refractory SCLC. The primary end-point was the response rate, while the secondary end-points were the toxicity profile and survival rate.

Patients and Methods

Patient selection. Patients who met all of the following criteria were considered eligible: a) histological or cytological proof of SCLC with no response to prior chemotherapy or progression after chemotherapy, b) measurable disease, c) most recent cytotoxic treatment less than 4 weeks before entry, d) ECOG performance status 0-2, e) age ≤75 years, f) adequate bone marrow function (leukocyte count ≥4,000/μl, hemoglobin level ≥9.0 g/dl and platelet count ≥100,000/μl), hepatic function (transaminases ≤2.5 times the upper limit of normal, bilirubin level ≤1.5 mg/dl), and renal function (creatinine ≤1.5 times upper limit of normal) and g) arterial oxygen partial pressure ≥60 torr. Excluded patients were those with any active concomitant malignancy, symptomatic brain metastases, a past history of drug allergy reactions, complication by interstitial pneumonia, treatment with non-steroidal anti-inflammatory drugs or steroids or other serious complications such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, massive pleural effusion or ascites or serious active infection. All patients gave written informed consent and our institutional review board for human experimentation approved the protocol.

Treatment schedule. Paclitaxel was infused intravenously (*i.v.*). over a 1-h period at a dose of 80 mg/m^2 each week for 6 consecutive weeks followed by a 2-week break. This 8-week period comprised one treatment cycle. Premedication consisted of 20 mg dexamethasone, 50 mg ranitidine and 50 mg diphenhydramine given *i.v.* 30 min prior to paclitaxel.

If the leukocyte count fell below 2,000/μl or the neutrophil count fell below 1,000/μl, recombinant granulocyte colony-stimulating factor (rhG-CSF) at a daily dose of 2 μg/kg was administered until the leukocyte count recovered to ≥10,000/μl, except on the days of paclitaxel administration. The toxicity assessment was based on the National Cancer Institute – Common Toxicity Criteria version 2.0. If grade 3 leukopenia, grade 4 neutropenia, grade 2 neuropathy or other grade 3 non-hematological toxicities occurred, the dose of paclitaxel in subsequent cycles was reduced by 10 mg/m^2 from the planned dose. Paclitaxel was not administered if the leukocyte count was <2,000/μl, the platelet count was <5,000/μl, or if there was grade 3 nausea/vomiting, infection with a fever of more than 38°C, or other grade 2 non-hematological toxicities except alopecia. The treatment was discontinued if there was disease progression, grade 3 neuropathy, other grade 4 non-hematological toxicities or a 2 consecutive weeks without paclitaxel administration.

Evaluation of response and survival. The tumor response was classified according to the WHO criteria (7). A complete response (CR) was defined as the total disappearance of all measurable and assessable disease for at least 4 weeks. Partial response (PR) was defined as a ≥50% decrease in the sum of the products of the 2 largest perpendicular diameters of all measurable tumors lasting for at least 4 weeks without the appearance of any new lesions. No change (NC) was defined as a decrease of <50% or an increase of <25% in tumor lesions for at least 4 weeks with no new lesions. Progressive disease (PD) was defined as the development of new lesions or an increase of 25% in the sum of the products of the 2 largest perpendicular diameters of all measurable tumors. The overall survival was measured from the time of study entry until death.

Statistical methods. The median probability of survival was estimated by the method of Kaplan and Meier (8). This study was designed as a phase II study, with the response rate as the main end-point. According to the Simons minimax design, with a sample size of 20 our study had a 90% power to accept the hypothesis that the true response rate was greater than 25%, while a 10% significance sufficed for rejection of the hypothesis that the true response rate was less than 5% (9).

Results

Patient characteristics. Between December 1999 and February 2002, a total of 22 patients were enrolled in the study, 1 of whom was deemed ineligible due to age (>75 years), leaving a total of 21 patients assessable for toxicity, response and survival. The main demographic characteristics of the cohort are summarized in Table I. The patient cohort consisted of 1 female and 20 males with a median age of 66 years (range, 48 to 75). Four patients exhibited limited disease and 19 exhibited extensive disease at the start of treatment. The majority of the patients had received no prior surgical treatment, while 67% had received prior radiation therapy. All patients had been treated with some form of cisplatin- or carboplatin-based combination chemotherapy regimen. Eighteen patients had received prior etoposide-containing chemotherapy and 10 prior irinotecan-containing chemotherapy. The median number of previous chemotherapy regimens administered was 1 (range, 1 to 2). Among the 10 patients who proved refractory to chemotherapy, 5 had NC or PD on first- or second-line treatment, 2 had PR but experienced disease progression during treatment and 3 had a relapse within a 90-day treatment-free interval after completing their treatments.

Toxicity. The toxicity of the regimen is summarized in Table II. Neutropenia was the main toxicity, with 6 out of the 21 patients experiencing grade 4 neutropenia during the entire study. Grade 3 anemia was observed in 2 patients. One patient experienced grade 4 anemia, secondary to digestive tract bleeding. Thrombocytopenia remained infrequent throughout the study. No cases of grade 3 or 4 thrombocytopenia were observed and there was no evidence of cumulative hematological toxicity.

Table I. *Baseline characteristics of all patients.*

Baseline characteristics		No. of patients
Sex	Male / Female	20 / 1
Age (years)	Median (Range)	66 (48-75)
ECOG PS	0/1/2	5 /12 /4
Disease extent	LD/ ED	4 / 17
Previous treatment	Chemotherapy only	4
	Chemotherapy + radiotherapy	14
	Chemotherapy + others	3
Previous chemotherapy	Platinum + etopoisde +/- others	18
	Including irinotecan HCl	10
	Others	1
No. of previous chemotherapy regimens	1 / 2 / 3	16 / 4 / 1
Response to prior chemotherapy	CR / PR / NC / PD / NE	2 / 13 / 5 / 0 / 1

No.: number
PS: performance status, LD: limited disease, ED: extensive disease.

Table II. *Toxicity of treatment for all cycles.*

Toxicity	No. of patients with event by grade				
	G0	G1	G2	G3	G4
Nausea	12	7	2	0	0
Vomiting	19	1	1	0	0
Diarrhea	17	3	1	0	0
Constipation	10	5	6	0	0
Mucositis	21	0	0	0	0
Gastric ulcer	20	0	1	0	0
Fever	16	3	2	0	0
Fatigue	13	0	8	0	0
Skin rash	20	0	0	1	0
Infection	18	0	0	3	0
Neuropathy	9	9	1	2	0
Myalgia	16	4	1	0	0
Dyspnea	17	0	1	2	1
Hemoglobin	1	9	9	1	1
WBC count	2	1	8	8	2
Neutrophil count	0	5	2	8	6
Platelet count	16	5	0	0	0
GOT	12	7	2	0	0
GPT	16	4	1	0	0
Total bilirubin	19	1	1	0	0

Other grade 3 and 4 toxicities included infection, skin rash, neuropathy and pulmonary toxicity. Grade 1 or 2 neuropathy was seen in 10 patients, and greater than grade 2 was observed in 2 individuals. No hypersensitivity reactions were encountered. Grade 3 or 4 pulmonary toxicity was reported in 3 patients and was characterized by dyspnea. Life-threatening complications of grade 4 infection and grade 4 dyspnea were encountered in 1 patient, who experienced febrile neutropenia and respiratory failure secondary to pneumonia after the third weekly dose. He was treated with antibiotics and supportive measures, but the respiratory distress worsened and he died on day 41. One of 2 grade 3 pulmonary toxicities was pneumonitis, probably induced by paclitaxel, but was resolved by steroid therapy.

Response to treatment and survival. The responses to therapy are shown in Table III according to whether the patient had primary refractory disease or primary sensitive cancer that subsequently relapsed. Although 1 out of the 21 patients was not assessable for response, having died during the first cycle, a ≥50% decrease in the sum of the products of the 2 largest perpendicular diameters of the tumor was achieved in this patient. Five of the 22 patients had a PR, but no CRs were observed and the overall response rate

Table III. *Response data.*

		No. of patients					Response rate (%)
		CR	PR	NC	PD	NE	
Total	21	0	5	4	11	1	23.8
Sensitive	11	0	3	3	5	0	27.3
Refractory	10	0	2	1	6	1	20.0

CI = confidence interval; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; NC = no change.

was 23.8% (95% confidence interval, 5.59 to 42.03). When only evaluable patients were included in the analysis, however, the response rate improved to 25% (95% confidence interval, 6.02 to 43.98). Two PRs (20%) occurred in refractory cases and 3 PRs (27%) were achieved in sensitive cases. Four patients showed no change, and 1 exhibited disease progression. The survival analysis was performed in January 2003, by which point 10 patients had died and 2 were still alive. The median survival time (MST) was 5.8 months and the 1-year survival rate was 13.4% (Figure 1).

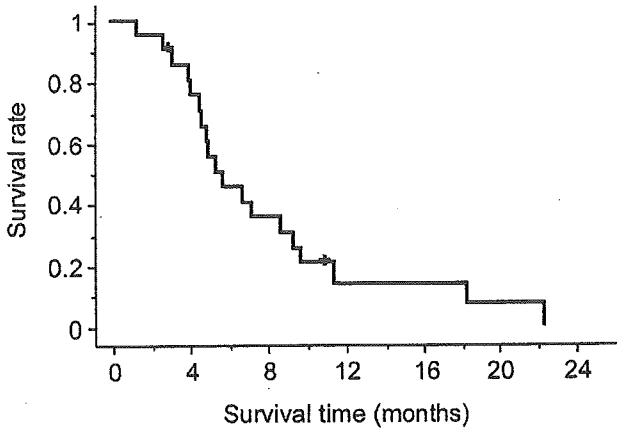

Figure 1. *Overall survival.*

Discussion

Since the outlook for SCLC patients who receive second-line therapy is poor, several new drugs, such as paclitaxel, docetaxel, gemcitabine, vinorelbine, topotecan and irinotecan, are currently under investigation. The new chemotherapy agents that have been most extensively evaluated in SCLC are the topoisomerase I inhibitors, including topotecan and irinotecan. Von Pawel *et al.* conducted a phase III study comparing single-agent topotecan with cyclophosphamide, doxorubicin and vincristine (CAV) in patients with progression at least 60 days after initial therapy and reported response rates of 24.3% for topotecan and 18.3% for CAV with a median survival time (MST) of 25.0 and 24.7 weeks, respectively, and found that topotecan was at least as effective as CAV in the treatment of patients with recurrent SCLC (10). Two studies of irinotecan in patients with refractory SCLC have been reported in Japan and the response rates in both studies were high, *i.e.*, 50% in 16 patients, and 47% in 15 patients, respectively (11, 12). We therefore consider that topoisomerase I inhibitors, such as topotecan and irinotecan, are key drugs in the second-line treatment of SCLC. However, the number of SCLC patients treated with an irinotecan-containing regimen as first-line chemotherapy has increased in Japan since, in a randomized phase III trial in Japan (13), a combination of irinotecan and cisplatin was shown to yield better survival than the standard etoposide and cisplatin regimen in patients with untreated extensive SCLC. Therefore, the search for effective drugs, other than topoisomerase I inhibitors, for previously treated SCLC, especially refractory SCLC, must be continued.

Single-agent paclitaxel, at a dose of 175 mg/m^2 as a 3-h infusion every 3 weeks in patients with previously treated SCLC, produced a response rate of 29% and an MST of 100 days (4). The results of our phase II study demonstrated that weekly paclitaxel at a dose of 80 mg/m^2 yielded a similar response rate of 23.8% and a much better MST of 5.8 months than that of paclitaxel given every 3 weeks. Because the antiproliferative activity of paclitaxel is cell-specific, prolonging patient exposure to a low dose of the drug beyond a threshold concentration is ultimately more efficacious than a short-term exposure to higher drug concentrations, a hypothesis supported by *in vitro* experiments with a variety of cell lines and suggested by the results of clinical studies. As clinical experience with paclitaxel treatment of various types of tumors has progressed, so has the use of weekly regimens at lower doses administered as 1-h infusions, as opposed to standard higher doses delivered once every 3 weeks as 3-h infusions.

A response rate of more than 10% is considered evidence of drug efficacy in previously-treated SCLC patients (14). Before newer drugs, such as topoisomerase I inhibitors, taxane, gemcitabine and vinorelbine were introduced, salvage chemotherapy did not usually prolong survival in SCLC and MSTs after relapse were 2.5 – 3.9 months (1). Single-agent phase II trials of gemcitabine, docetaxel and vinorelbine in patients with relapsed or refractory SCLC have been reported. Smyth *et al.* (15), using a 100 mg/m^2 dose of docetaxel, obtained a response rate of 25% in 28 assessable patients who had received prior chemotherapy. A trial of gemcitabine in 46 previously-treated patients yielded an 11.9% response rate (16) and vinorelbine provided response rates of 12% and 16% in second-line patients with sensitive disease (17,18). Thus, the MST of 5.8 months and response rate of 23.8% in this study compare favorably with those of published single-agent trials in relapsed or refractory SCLC.

The toxicity profile noted in this trial was predictable based on the toxicity profile previously described in weekly paclitaxel trials, neutropenia being the major toxic effect. All side-effects, except fatal neutropenic pneumonia in 1 case, were manageble. Grade 3 or 4 neutropenia occurred in 14 of the patients in our study but was immediately alleviated by treatment with G-CSF. Grade 3 or 4 anemia occurred in 1 patient, but there was no grade 3 or 4 thrombocytopenia in our study. The incidence of grade 3/4 myelosuppression was considered tolerable. There were 3 cases of grade 3 or 4 pulmonary toxicity, 2 of which occurred due to bacterial infection. This regimen required a dose of 20 mg of dexamethasone weekly as premedication. We believe that this occurrence of bacterial pneumonia might be related to the use of steroids.

Testing new drugs in previously-treated patients has the clear advantages of determining the degree of non-cross resistance with other drugs. Its greatest disadvantage is the risk of a considerable dose reduction (especially of myelotoxic drugs) to avoid extensive hematological side-

effects, perhaps resulting in doses that are too low to fairly evaluate the drug. Since a weekly administration of paclitaxel causes only mild myelosuppression and as there may be no cross resistance with platinum, etoposide, irinotecan, or topotecan, which are usually used to treat SCLC, we find this regimen suitable for previously-treated SCLC.

In summary, the weekly paclitaxel regimen is moderately effective in SCLC patients who have received prior chemotherapy. Based on the statistical design of this study, the 5 PR observed suggest that weekly paclitaxel warrants further evaluation in this patient population. Additional investigations will serve to clarify the role of this agent, either alone or in combination with other agents. Combining paclitaxel with other agents with proven non-cross resistance such as irinotecan, topotecan, or gemcitabine or new target-based agents is the next step needed to evaluate second-line situations, especially in patients with resistant disease.

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Irinotecan in the treatment of small cell lung cancer: a review of patient safety considerations

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A water soluble derivative of camptothecin, irinotecan (CPT-11) is effective against small-cell lung cancer (SCLC), as well as non-SCLC and gastrointestinal cancers. This extended review of recently concluded and ongoing studies focuses on irinotecan in the treatment of limited (LD) and extensive (ED) SCLC specifically considering the safety of patients. Irinotecan-induced diarrhoea is pervasive, and can be severe and life-threatening especially in combination with neutropenia. It can have a significant impact on patient quality of life, negatively influencing compliance with therapy and dose-intensity. For LD SCLC, irinotecan can be administered with radiotherapy concurrently or sequentially. In a Phase III study for ED SCLC comparing etoposide and cisplatin (EP) and irinotecan and cisplatin (IP) regimens, severe myelosuppression was more frequent in the EP arm than in the IP arm, and conversely severe or life-threatening diarrhoea was more frequent in the IP arm than in the EP arm. IP resulted in significantly higher response rates and overall survival in Japan, and confirmatory Phase III studies are ongoing. Irinotecan should not be administered to patients with any degree of ongoing diarrhoea above their baseline. Irinotecan can be administered with relative safety for patients with SCLC only through careful patient monitoring, especially regarding diarrhoea and myelosuppression.

Keywords: chemotherapy, irinotecan (CPT-11), radiotherapy, small-cell lung cancer (SCLC), toxicity

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1. Introduction

Lung cancer is the leading cause of cancer deaths worldwide, with > 900,000 deaths per year attributed to the disease [1]. About 15 – 20% of lung cancers are small-cell lung cancer (SCLC), although the frequency has been decreasing relative to other lung cancer over the last two decades [2]. SCLC is considered distinct from other non-small cell lung cancers (NSCLC) because of its clinical and biological characteristics [3]. The clinical characteristics of SCLC tend to be aggressive behaviour with rapid growth, early spread to distant sites, but more sensitive to chemotherapy and radiation. SCLC is usually staged as either limited disease (LD), in which the tumour is confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes, or extensive disease (ED), in which tumours have spread beyond the supraclavicular areas. About 30% of patients with SCLC have LD. Management of most cases of LD SCLC involves combination chemotherapy, usually with a platinum-containing regimen, and thoracic radiation therapy (TRT). If a complete response is obtained, the patient may be offered prophylactic cranial irradiation. The median survival time (MST) of LD SCLC is 16 – 24 months with current forms of treatment, such as chemoradiotherapy with or without surgery. ED SCLC patients are treated with combination

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chemotherapy, but the disease remains incurable. Usually a platinum-containing regimen is chosen. For ED SCLC, the MST is less than one year with currently available chemotherapy, and long-term survivors are still rare [4,5].

Furthermore, the prognosis is exceedingly poor for patients who receive second-line therapy after relapse. Response is influenced by the time to progression after cessation of first-line therapy. Patients who relapse less than three months after the completion of first-line therapy are termed refractory; they have response rates that are lower than for those patients who relapse more than three months after therapy, who are termed sensitive. The objective for these patients is palliation and increased quality of life, and therefore salvage therapy should be limited to patients with a good performance status (PS) and without significant comorbidities [3].

A water soluble derivative of camptothecin, irinotecan hydrochloride (CPT-11), a topoisomerase I inhibitor, has been synthesised for use in chemotherapy. The chemical structures of irinotecan and its major metabolites found in plasma are shown in **Figure 1**. Irinotecan is converted by hepatic and peripheral carboxylesterase to its active metabolite 7-ethyl-10-hydroxycamptothecin (SN38). This is subsequently glucuronidated by hepatic uridine diphosphate glucuronosyl transferase-1A1 (UGT 1A1), the enzyme responsible for bilirubin glucuronidation with multi-genetic variants, to SN38-glucuronide (SN38G) [6]. The patient with UGT1A1*28 has an impaired capacity for glucuronidation of SN-38, increased exposure to SN-38, and there is increased clinical toxicity when treated with irinotecan. To measure UGT1A1*28, in August 2005, FDA in the US cleared the Invader Molecular Assay for irinotecan dosing. However, irinotecan activity is not determined by the product of one gene [7]. Irinotecan, SN-38 and SN-38 glucuronide (SN-38G) may be shunted out of the cell via members of the ATP-binding cassette transporters [8]. The metabolism and pharmacogenetics of irinotecan is beyond the scope of this review, but there are some excellent reviews on this subject [9-11].

It should be cautioned that there are drug–drug interactions [12] with irinotecan. Exposure to irinotecan and its active metabolite SN-38 is substantially reduced in patients receiving the CYP3A4 enzyme-inducing anticonvulsants phenyntoin, phenobarbital or carbamazepine [13]. Rifampin, rifabutin and St. John's Wort are also CYP 3A4 inducers [14,15]. St. John's Wort is contraindicated during irinotecan therapy. Ketoconazole, a strong inhibitor of CYP3A4 [16], and contraindicated during irinotecan therapy, should be discontinued in patients at least one week prior to starting irinotecan therapy.

In Japan, 1245 cancer patients received irinotecan as a single agent in Phase I or Phase II trials that were conducted to obtain approval for commercial use from the Ministry of Health, Labour and Welfare. Of the 1245 patients, 55 (4.4%) died from toxicities of irinotecan, mainly myelosuppression and/or diarrhoea [17].

The onset of diarrhoea can occur early or be delayed beyond 24 h after injection of irinotecan. Early-onset diarrhoea is a cholinergic effect. Anticholinergic drugs, such as atropine, seem to easily reverse this side effect. Late-onset diarrhoea represents the dose-limiting toxicity (DLT) of irinotecan; it can be severe and life-threatening, especially in combination with neutropenia. Late-onset diarrhoea is treated with loperamide, and identification of high-dose loperamide as an effective remedy for this toxic effect greatly facilitated development of irinotecan [18,19]. These studies established the usefulness of high-dose loperamide. Patients should be instructed to take high-dose loperamide at the first onset of any irinotecan-associated late-onset diarrhoea that has occurred at least 12 h after drug administration. This therapy has been widely used for the management of diarrhoea caused by irinotecan.

For the treatment of SCLC, initial irinotecan is usually administered on days 1 and 8 every 3 weeks or on days 1, 8 and 15 every 4 weeks. The dose ranges from 50 to 70 mg/m^2 when administered weekly. As an example of the dose modification of irinotecan, Kudoh *et al.* [20] used the following dose modification: irinotecan is not given on days 8 or 15 if the leukocyte or platelet counts were < 3000/μl or < 75,000/μl, respectively. It is also withheld if the patient develops diarrhoea of grade 2 (increase of 4 – 6 stools/day, or nocturnal stools) or worse (grade 3: increase of > 6 stools/day or incontinence; grade 4: physiological consequences requiring intensive care). The next course of treatment can only be initiated if the leukocyte count is ≥ 4000/μl, the platelet count is ≥ 10,000/μl, serum creatinine is less than the upper limit of normal, and diarrhoea has been resolved. There is no dose modification for the leukocyte count, platelet count or diarrhoea during the same course. The dose of irinotecan in the next course was reduced by 10 mg/m^2 if the leukocyte count was < 2000/μl, the platelet count was < 50,000/μl, or diarrhoea was grade 3 to 4. This dose modification was applied in most studies with minor variation. For example, in some studies, the delay in the irinotecan doses was applied when the leukocyte count was < 2000/μl [21] instead of 3000/μl.

Another available topoisomerase-I inhibitor, topotecan, has achieved response rates of up to 22% in previously treated patients with SCLC and survival almost double that achieved with other single agents. Compared with cyclophosphamide/doxorubicin/vincristine (CAV), single-agent topotecan achieved a higher response rate, longer survival and statistically significant improvements in dyspnoea, hoarseness, fatigue, anorexia and interference with daily activities [22,23]. The incidence of grade 3 – 4 diarrhoea was extremely low (1%). The clinical comparison of these two topoisomerase-I inhibitors has not been tried. This review focuses mainly on the recent results of irinotecan in the treatment of SCLC in connection with patient safety considerations.

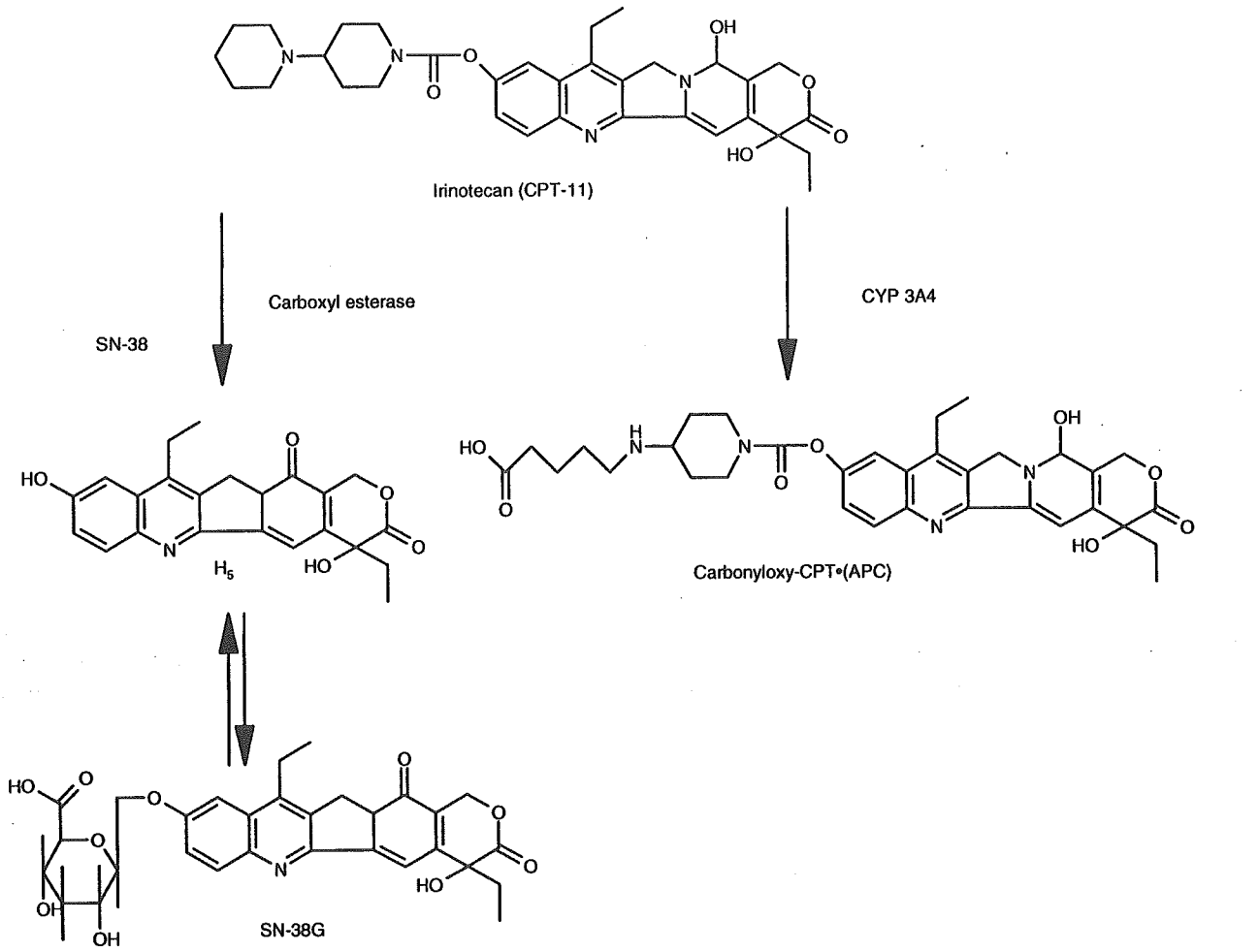

Figure 1. Metabolism of irinotecan. Chemical structures of CPT-11 and its major metabolites.

2. Irinotecan containing regimens as front-line treatment

2.1 Irinotecan plus cisplatin for ED SCLC

Clinically, irinotecan was proved to be effective against SCLC [24]. Negoro *et al.* have demonstrated that 13 (37%) out of 35 patients responded, including 33% of previously treated patients and 50% of chemotherapy-naive patients. In a Phase II trial of irinotecan for previously treated SCLC, the response rate was 47% out of 16 patients [25].

IP was tested in a Phase II trial for patients with previously untreated SCLC [20]. A total of 40 patients (53%) had LD and 35 patients (47%) had ED. Initially, irinotecan 80 mg/m^2 over 90-minutes infusion was given on days 1, 8 and 15, and cisplatin 60 mg/m^2 was given every 4 weeks. After 3 of the initial 10 patients experienced severe haematological toxicity, diarrhoea and hepatic toxicity, and one patient died of diarrhoea and neutropenia, the irinotecan dose was reduced to 60 mg/m^2. The response rate was 84%, with a complete response rate of 29%. The MST was 14.3 months for LD patients and 13.0 months for ED patients, an encouraging result. Although the survival of LD was not increased significantly, this may be due to the small number of LD SCLC patients accrued. This study prompted a Phase III study of the Japan Clinical Oncology Group (JCOG 9511).

The JCOG conducted a multi-centre, randomised, Phase III study which compared irinotecan plus cisplatin with etoposide plus cisplatin (EP) in patients with ED SCLC (JCOG 9511) (**Figure 2**) [26]. IP consisted of four 4-week cycles of 60 mg/m^2 of irinotecan on days 1, 8 and 15, and 60 mg/m^2 of cisplatin on day 1. The regimen of etoposide and cisplatin consisted of four 3-week cycles of 100 mg/m^2 of etoposide on days 1, 2 and 3, and 80 mg/m^2 of cisplatin on day 1. The delivered dose intensity for irinotecan was 80%. The results are listed in **Table 1**. This study was terminated early because an interim analysis found a statistically significant difference in survival between the two arms. The MST was 12.8 months in the IP arm and 9.4 months in the EP arm ($p = 0.002$). At two years, the proportion of patients surviving was 19.5% in the IP group and 5.2% in the EP

Table 1. IP versus EP in phase III studies.

	IP	EP	p-value	IP	EP	p-value
	JCOG9511 study [26]			*Hanna's study* [27]		
	(n = 75)	(n = 77)		(n = 210)	(n = 104)	
Irinotecan: delivered dose intensity	80%			90%		
Survival						
Median survival time (months)	12.8	9.4	0.002	9.3	10.2	0.6226
1-year survival (%)	58.4	37.7		35.4	36.7	
2-year survival (%)	19.5	5.2		8.0	7.9	
Haematological						
Neutropenia	65.3	92.2	< 0.001	36.2	86.5	< 0.0001
Anaemia	26.7	29.9	0.72	4.8	11.5	< 0.0268
Thrombocytopenia	5.3	18.2	0.002	4.3	19.2	< 0.0001
Nonhaematological				(n = 216)	(n = 106)	
Diarrhoea	16	0	< 0.001	21.3	0	0.0001
Response				(n = 221)	(n = 110)	
Complete response	2.6	9.1		3.6	2.7	
Partial response	81.8	58.4		44.3	40.9	
Overall response	84.4	67.5	0.02	48.0	43.6	
Stable disease	2.6	20.8		4.1	7.3	
Progressive disease	3.9	11.7		20.0	20.0	
Not evaluable	6.5	0		28.1	29.1	

EP: Etoposide and cisplatin; IP: Irinotecan and cisplatin.

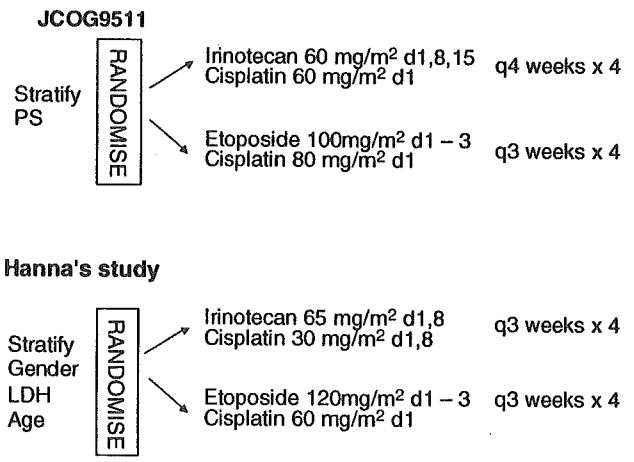

Figure 2. Two Phase III randomised trials.
LDH: Lactate dehydrogenase.

group. This was the first study to show the superiority of any one regimen over etoposide plus cisplatin for the front-line treatment of ED SCLC, and IP has become one of the standard regimens for ED SCLC in Japan. Severe myelosuppression was more frequent in the EP group than in the IP group. On the other hand, severe diarrhoea was more frequent in the IP arm than in the EP arm. Despite the dose modifications, major deviations from the protocol resulted in failure to reduce the dose of chemotherapy (in 6 patients); administration of irinotecan despite the presence of grade 1 (increase of < 4 stools/day) or 2 diarrhoea (in 9 patients); continuation of the study treatment despite grade 2 to 3 pulmonary toxicity (in 3 patients); and continuation of the treatment despite grade 3 hepatic toxicity (in 1 patient). There were 3 treatment-related deaths in the IP arm; one patient died of bleeding from a metastatic site in the lung, another patient died of sepsis associated with neutropenia and diarrhoea, and the third patient died of pneumonia associated with neutropenia. These three treatment-related deaths in the IP arm occurred during the first or second cycle of treatment and were attributed to haematological toxicities of the first cycle. This may indicate that severe haematological toxicities, as well as diarrhoea, during the first cycles of chemotherapy should be managed carefully. All cases of grade 1 to 4 diarrhoea occurred during the first and second cycles of the IP arm but early suspension of treatment may have prevented death associated with diarrhoea in all but one patient, which

involved a protocol violation because the patient was given irinotecan on day 8 of the first cycle despite the presence of grade 1 diarrhoea. This suggests that irinotecan should not be administered to patients with any degree of ongoing diarrhoea above their baseline.

Confirmatory studies are underway; currently, there is only one concluded study showing IP superiority, but it had a small sample size. Additionally, pharmacogenomic differences may exist between Japanese and Western populations.

Hanna *et al.* presented a Phase III trial comparing IP with EP in patients with previously untreated ED SCLC at the ASCO meeting in 2005 (Figure 2, Table 1) [27]. This was designed to confirm the JCOG9511 trial. However, the dose and schedule were modified to increase dose intensity.

The IP arm consisted of cisplatin 30 mg/m^2 and irinotecan 65 mg/m^2 on days 1 and 8 every 3 weeks. The EP arm was cisplatin 60 mg/m^2 on day 1, and etoposide 120 mg/m^2 on days 1 – 3 every 3 weeks for 4 cycles, or disease progression, or intolerable toxicity. This was planned to improve tolerability, achieve greater dose intensity and maintain or improve efficacy. The 336 patients were stratified by gender, lactate dehydrogenase level and age, and were randomised in a 2:1 fashion, with 221 treated with IP (median age, 63 years; range, 37 – 82 years; male, 57.5%) and 109 to EP (median age, 62 years; range, 38 – 83 years; male, 57.3%). Baseline characteristics were well balanced across the 2 arms, with a high representation of PS of 0 or 1 (IP, 92.3%; EP, 88.2%). After 30 patients with PS 2 were enrolled, study amendment excluded PS 2 patients. Delivered dose intensity of irinotecan was 39 mg (94%), higher than that of the JCOG9511 trial (80%). In both arms, 65% of patients received 4 or more cycles. Selected grade 3 or 4 toxicities in IP versus EP arm were: diarrhoea (21 versus 0%), neutropenia (35 versus 84%), febrile neutropenia (4 versus 11%). Grade 3 or 4 haematological toxicities were significantly more common with EP than IP. There was a trend towards more febrile neutropenia in the EP arm (10 versus 4%), and significant differences were seen in rates of dehydration (13 versus 3%; $p = 0.15$), vomiting (13 versus 4%; $p = 0.0445$), and diarrhoea (21 versus 0%; $p < 0.0001$). The survival of EP in both trials was similar (MST: 10.2 months in this study and 9.4 months in the JCOG9511 trial). However, the MST of IP was 9.3 months in this trial and 12.8 months in the JCOG9511 trial. Differences in outcome of this study from the JCOG trial may be due to pharmacogenomic or patient characteristic differences, or a change in the dose/schedule of IP. Pharmacogenomic studies among ethnic populations are needed to address this issue. It is likely that IP will prove to be at least as effective as other treatments for patients with ED SCLC.

Other Phase III trials will clarify these issues, including a SWOG S0124-randomised Phase III trial with the dose and schedule of each arm the same as the JCOG9511 trial, and a Phase III study started in June 2002 – (NCT00143455) sponsored by Pfizer. In this second study, IP consists of irinotecan 65 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1. EP consists of etoposide 100 mg/m^2 on days 1 – 3 and cisplatin 80 mg/m^2 on day 1 every 3 weeks. The results of these studies are awaited.

The debate continues regarding the optimal dose of combination chemotherapy as related to improvement of the outcome of SCLC. However, the author can state that too low a dose intensity may lead to poor results. Takigawa *et al.* used fractionated administration of IP in 15 patients with ED SCLC [28]. Both irinotecan at a dose of 50 mg/m^2 and cisplatin at a dose of 60 mg/m^2 were given on days 1 and 8, and repeated every 4 weeks up to 4 cycles. Although objective response rates were 80%, no complete response (CR) were obtained. The MST was 9.4 months and one-year survival was 40.0%. They stopped enrollment because of no CR and poor survival compared to Kudoh's data [20]. The dose intensity may be low because this regimen had a lower dose of irinotecan (50 mg/m^2) and a two-week rest period.

Han *et al.* reported a Phase II study of dose-intensified weekly IP in chemo-naive patients with ED SCLC [29]. The initial six patients received cisplatin 50 mg/m^2 followed by irinotecan 90 mg/m^2 on day 1 and 8 of a 21-day cycle (level I), with one treatment death and three febrile neutropenias. The doses of cisplatin and irinotecan were then reduced to 40 mg/m^2 and 80 mg/m^2, respectively (level II). The overall response rate was 97%, with a complete response rate of 26%. The MST was 11.1 months and 1- and 2-year survival rates were 44.1% and 11.8%, respectively. Major grade 3 or 4 toxicities included neutropenia (89%), anaemia (59%) and diarrhoea (27%). There were three treatment-related deaths, occurring in elderly patients aged > 60 years and/or relative poor baseline PS 2 or 3. Although they adopted the oral alkalisation and control of defecation to prevent irinotecan-induced side effects, especially delayed diarrhoea, they are uncertain whether or not this preventive treatment reduced the observed incidence of severe delayed diarrhoea.

2.2 Irinotecan plus carboplatin for ED SCLC

Schmittel *et al.* studied the DLT and maximum tolerated dose (MTD) of a dose escalation of carboplatin to a fixed dose of irinotecan (IC) in Caucasian patients [30]. They demonstrated that the maximum tolerated dose is irinotecan 50 mg/m^2 administered on day 1, 8 and 15, and carboplatin at an area under the concentration–time curve (AUC) of 5 mg/ml x min, on day 1 of a 4-week cycle. DLT (neutropenia, thrombocytopenia and diarrhoea) was comparable to the results of the Japanese trial at a dose of 60 mg/m^2 of irinotecan and AUC = 5 of carboplatin [31].

Subsequently, Schmittel *et al.* presented a randomised Phase II trial comparing IC and etoposide plus carboplatin (EC) in ED SCLC [32]. Chemotherapy-naive ED SCLC patients were randomly assigned to receive carboplatin AUC = 5 either in combination with 50 mg/m^2 of irinotecan on days 1, 8 and 15 or with etoposide 140 mg/m^2 on days 1 – 3. In the IC arm, treatment was repeated every four weeks; in the EC arm, every

three weeks. IC improved response rate (10% CR and 61% partial response (PR) in IC, 0% CR and 50% PR in EC) and progression free survival (9 months, p = 0.03) over standard EC (6 months). The MST was 12 months in the IC arm and 10 months in the EC arm, but with no significant difference. Patients with EC had significantly higher incidence of grade 3 to 4 leucopenia, neutropenia and thrombocytopenia. Grade 3 – 4 diarrhoea developed more frequently in the IC arm (11 versus 6%), but with no significant difference. Haematotoxicity was favourable in the IC arm. They extended into a randomised Phase III trial to assess impact on overall survival, and concluded this study showed that even when carboplatin is used instead of cisplatin, the survival of IC and EC was not significantly different, and that myelosuppression was more frequent in EC than IC.

2.3 Irinotecan plus etoposide for ED SCLC

A Phase II study of irinotecan and etoposide (IE) for chemotherapy-naive ED SCLC was recently conducted without platinum by the West Japan Thoracic Oncology Group (WJTOG) [33]. A total of 50 patients were enrolled. This regimen consisted of irinotecan 60 mg/m^2 on days 1, 8 and 15, and etoposide 80 mg/m^2 on days 2 – 4. The overall response rate was 66% with a complete response rate of 10%. The MST was 11.5 months and the 1-year survival rate was 43.2%. Grade 3 – 4 neutropenia, thrombocytopenia and diarrhoea were 62.9, 4 and 2%, respectively. There was no treatment-related death. This regimen seems to be equal to the EP regimen. The dose intensity of irinotecan and etoposide achieved with this regimen was not adequate. This may be the reason for the low incidence of diarrhoea (2%). A schedule of irinotecan administered on days 1 and 8 at 3-week intervals may be preferred.

2.4 Triplets including irinotecan for ED SCLC

JCOG9902-DI was a randomised Phase II trial to compare two kinds of three-drug combinations of cisplatin, etoposide and irinotecan (PEI regimens) for the treatment of ED SCLC [34]. A total of 60 patients were randomised to receive either arm A (cisplatin 25 mg/m^2 on day 1, on weeks 1, 3, 5, 7 and 9 and etoposide 60 mg/m^2 on days 1 – 3, on weeks 2, 4, 6, 8), or arm B (cisplatin 60 mg/m^2 on day1, irinotecan 60 mg/m^2 on days 1, 8, 15 and etoposide 50 mg/m^2 on days 1 – 3, every week for 4 cycles). Prophylactic G-CSF support was provided in both arms. This study suggested that the PEI combinations in both schedules have significant activity against ED SCLC with acceptable toxicity. The CR rate of 17% and MST of 12.9 months in arm B were much more promising compared with the CR rate of 7% and MST of 8.9 months in arm A. They concluded that arm B should be selected for future Phase III studies. However, because irinotecan administration often needed to be skipped, especially on day 15, they suggested a 3-week schedule in which irinotecan is administered only on days 1 and 8.

Briasoulis *et al.* showed that irinotecan can be safely combined with cisplatin and etoposide in a convenient and simple schedule of administration over three days [35]. They treated 36 patients with irinotecan on day 1 in combination with fixed doses of cisplatin (20 mg/m^2) and etoposide (75 mg/m^2), both for 3 consecutive days. Irinotecan dose was escalated from 60 mg/m^2 by increments of 40 mg/m^2 in this Phase I trial. The MTD of irinotecan was 140 mg/m^2 and the recommended optimal dose 120 mg/m^2. DLTs were febrile neutropenia and grade 3 diarrhoea. This same regimen is being studied with concurrent TRT in a total dose of 54 Gy in 30 fractions (1.8 Gy once daily) [36].

Thompson *et al.* reported a Phase II trial of the Minnie Pearl Cancer Research Network at the 2005 ASCO meeting [37]. They added a molecular targeted agent, imatinib (60 mg/day, per os) to chemotherapy of irinotecan (60 mg/m^2 on days 1, 8 and 15) and carboplatin (AUC = 4) every 4 weeks. Imatinib targets c-kit expression. Grade 3/4 haematological toxicity included: neutropenia (29%/16%), anaemia (13%/1%) and thrombocytopenia (7%/0%). The response rate was 66% with 10% CR. Grade 3 diarrhoea was observed in 21%. There were no treatment-related deaths. The MST was 8.5 months. This suggests that C-kit expression did not correlate with survival and that imatinib offers no efficacy at a cost of increased toxicity when combined with irinotecan and carboplatin in the treatment of ED SCLC.

3. Irinotecan-containing regimens for relapsed or refractory SCLC

Huisman *et al.* have summarised 21 Phase II studies and 3 randomised trials of second-line chemotherapy in patients with SCLC reported from 1989 to 1999 [38]. They found a cumulative response rate of 21% for multi-drug regimens and 19% for single agents. As yet there is no standard second-line treatment established for patients with SCLC who fail or relapse after front-line treatment.

Irinotecan was combined with various anticancer drugs in doublet or triplet. As doublets, these include cisplatin [39], weekly or every three weeks carboplatin [40,41], etoposide [42], gemcitabine [43,44], ifosfamide [45] and paclitaxel [46]. The responses vary from 10 to 94%, and the MST ranges from 5.8 to 8.9 months. As described earlier on triplet including irinotecan [34,47], a three-drug combination Phase II study of irinotecan, cisplatin and etoposide (PEI regimen) was conducted only for sensitive relapsed SCLC (40 patients) [48]. This Phase II regimen consisted of cisplatin 25 mg/m^2 weekly for 9 weeks, etoposide 60 mg/m^2 for 3 days on weeks 1, 3, 5, 7 and 9, and irinotecan 90 mg/m^2 on weeks 2, 4, 6 and 8 with G-CSF support after day 1 on week 2. The results showed a response rate of 78% (CR rate of 13%) and the MST of 11.8 months. A total of 39 patients (98%) had a good PS of 0 or 1. Grade 3 – 4 neutropenia, thrombocytopenia, and diarrhoea were observed in 73, 33, and 8%, respectively. Nonhaematological toxicities were mild and transient.

Another three-drug combination of cisplatin, ifosfamide and irinotecan with G-CSF was conducted by Fujita *et al.* [49].

The response rate was 94.4% and the MST was 11.1 months, encouraging result. Because of patient selections, it is difficult to make wholly valid conclusions about the most effective regimen based only on Phase II results. However, three-drug combinations containing irinotecan with G-CSF support may have better survival and feasibility than the doublets. The disadvantage is that triplet regimens require G-CSF support, which may make out-patient treatment difficult.

4. Irinotecan containing regimen for LD SCLC

Two meta-analyses showed that the addition of TRT to chemotherapy in patients with LD SCLC improves survival at two and three years by 5.4% [50,51]. In these meta-analyses, non-platinum-based combination chemotherapies were commonly used, with only a few trials using platinum-based chemotherapy. Cisplatin and etoposide plus TRT is now widely regarded as the standard regimen for LD SCLC, and presents acceptable toxicity [52]. Turrisi *et al.* reported results of once-daily versus twice-daily (b.i.d) TRT with four cycles of cisplatin and etoposide. Results showed that the MST was significantly superior in the b.i.d arm (23 versus 19 months) [53].

Irinotecan showed potent radiosensitising effects in human lung tumour xenografts which were related to the cell cycle [54]. Kubota *et al.* reported a pilot study of concurrent etoposide and cisplatin plus accelerated hyperfractionated TRT followed by irinotecan and cisplatin for LD SCLC (JCOG9903) [21]. Treatment consisted of etoposide 100 mg/m^2 on days 1 – 3, cisplatin 80 mg/m^2 on day 1, and concurrent b.i.d TRT of 45 Gy beginning on day 2. The IP regimen started on day 29 and consisted of irinotecan 60 mg/m^2, days 1, 8, 15 and cisplatin 60 mg/m^2 on day 1, with three 28-day cycles. A total of 31 patients were accrued. Although a pilot study, the MST was 20.2 months and 1-, 2- and 3-year survival rates were 76%, 41%, and 38%, respectively. This encouraging regimen proved safe with acceptable toxicities. A randomised Phase III trial comparing EP with IP following EP plus concurrent TRT for LD SCLC is now underway (JCOG0202).

The WJTOG also conducted a similar regimen [55]. Treatment included cisplatin 80 mg/m^2 on day 1 and etoposide 100 mg/m^2 on days 1 – 3 with concurrent TRT (1.5 Gy/b.i.d, a total dose of 45 Gy) followed by 3 cycles irinotecan 60 mg/m^2 on days 1, 8 and 15 and cisplatin 60 mg/m^2. The results of 51 patients were almost identical to JCOG9903; overall response and CR rate was 87.8% and 40.8%, respectively; Grade 4 toxicity included neutropenia (83.7%), anaemia (10.2%), thrombocytopenia (0%), diarrhoea (2%) and infection (2%); the MST was 21.5 months and 2-year survival rate was 45.7%.

A Phase II study of IP induction followed by concurrent b.i.d TRT with EP chemotherapy for LD SCLC was conducted [56] and also showed encouraging results. Treatment consisted of two cycles of cisplatin 40 mg/m^2 and irinotecan 80 mg/m^2 on days 1 and 8 of a 3-week cycle. This was followed by two 3-week cycles of cisplatin 60 mg/m^2 on days 43 and 64, and etoposide 100 mg/m^2 on days 43 – 45 and 64 – 66, with concurrent b.i.d TRT total of 45 Gy beginning on day 43. Thirty-five patients were accrued. The MST was 25 months (but it should be noted that this is a single institution Phase II study).

In these studies, irinotecan was used on an induction or adjuvant setting, and both regimens were encouraging. However, randomised study in which both modalities are compared has not been conducted.

There have been a few trials of concurrent chemoradiotherapy including irinotecan for patients with SCLC as well as NSCLC. Recently, a combined modality treatment of IC and TRT followed by bevacizumab (antiangiogenic anti-VEGF antibody) in the treatment of LD SCLC was conducted in a Phase II trial by the Minnie Pearl Cancer Research Network [57]. Induction therapy consisted of irinotecan 50 mg/m^2 on days 1 and 8, carboplatin AUC = 5 on day1, TRT 1.8 Gy single daily dose to total dose of 61.2 Gy (34 fractions), beginning with the 3rd cycle. Chemotherapy was repeated every three weeks for four cycles. As a maintenance therapy, bevacizumab 10 mg/kg i.v. every 2 weeks was given until disease progression, or a maximun of 10 doses (20 weeks) were administered. The response rate was 81% with 28% CR. This regimen was well tolerated with rare grade 4 toxicity and no treatment-related deaths. One-year progression-free and overall survival were 68% and 71%, respectively. These results suggest that irinotecan can be safely administered with TRT concurrently.

Sohn *et al.* also reported a Phase II study of IP with concurrent TRT in LD SCLC [58]. Chemotherapy of irinotecan 60 mg/m^2 on days 1, 8 and 15 and cisplatin 40 mg/m^2 on days 1 and 8 were repeated every 4 weeks until a maximum of 6 cycles. TRT of 2 Gy/day was commenced on day 1 of the second chemotherapy cycle up to a total of 54 Gy. The results are not concluded at this time.

Langer *et al.* reported a Phase I study of IP and either b.i.d TRT (45 Gy) or once daily RT (70 Gy) to determine if irinotecan can be safely integrated with concurrent TRT and cisplatin in LD SCLC [59]. Acute DLT was defined as grade 4 oesophagitis, pneumonitis, or diarrhoea; grade 4 neutropenic fever; or any attributable grade 5 fatal toxicity (≤ 90 days after RT). Although preliminary, there has been no attributable DLT in the 26 patients that have been enrolled. In combination with cisplatin 60 mg/m^2 every 3 weeks x 4 and either b.i.d TRT or once daily TRT, irinotecan 40 mg/m^2 on days 1 and 8 was safe and feasible. Irinotecan at 50 mg/m^2 on days 1 and 8 every 3 weeks x4 was also feasible in combination with cisplatin and b.i.d TRT. These reports allow us to conclude that irinotecan can be administered with radiotherapy sequentially or concurrently.

5. Expert opinion and conclusion

Irinotecan is effective against SCLC. For the treatment of ED SCLC, IP regimen is at least comparable to EP regimen.