厚生労働科学研究費補助金

医療技術実用化総合研究事業

ホウ素中性子捕捉療法(BNCT)を用いた悪性胸膜中皮腫に対する効果的治療法の開発研究

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研究代表者　小野　公二

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総合研究報告書

ホウ素中性子捕捉療法(BNCT)を用いた悪性胸膜中皮腫に対する効果的治療法の開発に関する研究

研究代表者　　小野公二　京都大学原子炉実験所・教授

研究要旨
悪性胸膜中皮腫は病巣の三次元形状が複雑で、重粒子線治療でも巧く治療することはできない。BNCTは細胞選択的放射線照射が可能な治療法で斯うした腫瘍は良い標的になると考えられる。これまでのBNCTの経験やX線治療の経験に基づいて臨床研究の計画書を作成し、各施設の倫理委員会より実施の承認を得た。４例に試験的にBNCTを実施し、腫瘍マーカーの低減、症状の緩和を得た。外、X線治療例での正常肺組織に対する損傷の観察から耐容線量の推定を行った。更に、ホウ素化合物に対する単クローン抗体によるELISA法で簡便、正確に血竣中のホウ素化合物濃度を測定するシステムを確立した。更に本抗体を用いて、ホウ素化合物BPAとBSHの細胞内のミクロ分布を検索し、その性質の相違を確認した。次世代の中性子源として加速器(サイクロトロン)中性子源の開発を進め、検証可能な強度に到達したビームの物理学的・放射線生物学的特性を確認した。中性子の分布と強度は京大原子炉のそれよりも良く、RBEはやや小さかった。

研究分担者
中川和彦・
近畿大学医学部内科学腫瘍内科部門教授
中野孝司・
兵庫医科大学内科学呼吸器RCU科・主任教授
平塚純一・
川崎医科大学医学部放射線医学(治療)教授
奥村明之進・
大阪大学大学院医学系研究科外科系臨床医学教授
切畑光統・
大阪府立大学大学院生命環境科学研究科教授
櫻井良憲・
京都大学原子炉実験所准教授

A．研究目的

悪性胸膜中皮腫はアスベストへの暴露に起因して発症し、我が国では今後10万人に及ぶ犠牲者が予測されながら十分に有効な治療法が開発されていない。進行期には病巣が複雑な三次元形状を呈するため、今日の高精度放射線治療の技術をもってしてもその応用が困難で放射線治療の役割は限定的であり、斬新なアイデアの放射線治療が切望されている。ホウ素中性子捕捉療法(BNCT)ではホウ素(B-10) 原子核が中性子を捕獲する反応に伴い細胞径を超えない飛程のα粒子が放出される。従って、ホウ素化合物が癌A細胞に選択的に集積すれば選択的に癌細胞に線量を集中できる。更にα粒子の生物効果は非常に大きく、α粒子が細胞核に届けば細胞破壊は確実である。京大炉では腫瘍細胞で充進しているアミノ酸輸送により高濃度で集積するホウ素化合物BPAを用いて高度進展の悪性胸膜中皮腫に対するBNCTを実施し、腫瘍の縮退と速やかな症状(激しい肋間神経痛}の消失が得られた症例を経験した。BPAの腫瘍での集積の程度は18F-BPAPETで事前に検索できる。正常肺のX線耐容線量と体積の関係は解明されており、血中ホウ素濃度と中性子数から計算できる物理線量をX線等価生物線量に変換する係数も報告されている。以上から、これらの実績と諸報告を踏まえて本研究を推進し、悪性胸膜中皮腫を対象にした加速器中性子BNCTの治療の基礎を固めることを目的とする。また、本研究を通じて同様に複雑な腫瘍形状を呈する、有効な治療法の見出されていない他の進行期癌に対する治療法の開拓にも繋げることも目的とする。

B．研究方法

BNCT研究は臨床研究者、放射線生物学に精通した研究者、ホウ素化合物に係る有機化学者、医学物理学者による学際的共同研究により始めて効果的な研究体制が構築できる。そこで、各分野の専門家による研究集団を組織した。「肺中皮腫に対するBNCT効果とホウ素化合物集積及びその向上の研究ならびに研究の総括」「肺中皮腫に対するBNCT効果および抗癌剤併用効果の検索」「肺中皮腫および正常肺組織に対する効果を検索」「ホウ素化合物BPAとBSHの簡便なホウ素濃度測定技術の開発」更に、「肺における中性子分布の改善

照射技術の改良の研究」の課題を分担して研究を進めた。

1. 臨床研究者を中心に神戸市の臨床研究情報センターCTRI)の支援を受け、悪性胸膜中皮腫のBNCT臨床試験研究(多施設共同)計画を作成した。ホウ素化合物の腫瘍集積の程度の予測、特に血中濃度に対する比は重要であるが、悪性胸膜中皮腫に対する18F-BPAPETの経験の蓄積は極めて少ない。エントリー基準を考え、決める上で集積能の実態を把握することは不可欠である。18F-BPAPET可能な京都の病院の協力を得てデータを集積した。
2. 新たな補助治療法の開発の為、中皮腫の予後を支配する諸因子（血清マーカーなど）の探索を行った。
3. 正常肺組織の耐容線量を検討した。更に、アスベスト暴露が肺組織内の炎症反応、免疫反応に与える影響を調べることで、アスベスト暴露がベースにある中皮腫患者で、放射線誘発肺臓炎（線維症）の発生頻度が高まるかどうかを検討した。
4. 癌幹細胞(Cancer stem cell)と遊離癌細胞 Isolated cancer cell に注目して研究を行った。
5. 棚素化合物(BPA)の簡便な測定法は実際のBNCTを実施する際に非常に重要で、従来の手法はホウ素原子の濃度を測定する方法で、あった。しかし、生体内でホウ素化合物が分解するとホウ素原子の分布とホウ素化合物の分布には差が生まれる。そこで、ホウ素化合物自体を測定する手法を考案し、実験動物での精度を検証した。特に、本研究では実験犬や再稼働したKURでのBNCT患者(脳腫瘍、頭頸部癌)の試料で有用性を確認した。
6. BNCTは将来に加速器中性子源によって承認された実医療とする必要がある。京都大学原子炉実験所では加速器(サイクロトロン)中性子源と照射システムの開発を企業との共同で進めており、ビーム強度の物理・生物学特性を培養細胞とマウス(担癌および非担癌)を用いて、コロニー形成能、微小核形成能、マウス放射線口腔死、骨髄損傷、腫瘍の増殖遅延などを指標として評価した。
7. BNCT用線量評価手法を検討した。「多重即発γ線テレスコープシステム」と「QA用ファントム」の胸膜中皮腫BNCTへの適用に関する検討を行った。「γ線テレスコープシステム」は、従来、肝腫瘍BNCTにおける線量評価のために設置したものであり、生体中の組織に含まれる水素と中性子との反応により発生する2.22MeVの即発γ線と、投与した薬剤注の硼素10と中性子との反応により発生する478keVの即発γ線を計数することで、照射時の硼素10濃度を定量化するためのものである。硼素10の代わりに多数の即発 γ 線を発生する Gd 等を利用することで、濃度だけでなく、即発 γ 線の発生位置に関する情報も得られる可能性がある。「QA ファントム」に関しては、検出器の性能の限界により困難であった中高エネルギー中性子に関する線量評価を、ファントムの材質の工夫により改善を検討した。低エネルギー中性子に対して吸収の大きいリチウム 6 を適度に水等のファントム材に混ぜることで、中高エネルギー中性子の分布を際立たせることを考案した。QA ファントムに関するシミュレーションは、モンテカルロコード”MCNP”を用いて行った。

（倫理面への配慮）

本研究の計画は各施設の倫理委員会でその実施の承認を得た上で実施する。更に、各症例に関して、原子炉実験所の症例審査委員会で適否の審査を受け、その上で承認された後に実施することと規定している。斯うして対象者に十分な倫理的配慮を行うとともに、不利益の及ばないようにした。

C．研究結果

1．本臨床試験には7例が登録された。予想と異なり、F-BPA PETでのT/B値が適応基準に到達せず、2回目の検査を待たねばならなかった。再検査を実施出来た4例で、BNCTを実施した。胸部痛などの症状が低減するなど効果が認められた。一方、正常肺にはBNCTによる有害事象は発生しなかった。唯、一例で2回目の照射の後に発熱と血圧低下の副作用が出現したため重篤な有害事象(SAE)として研究事務局に報告した。精査にてSAEの原因は尿路感染症による敗血症と診断し、抗生物質による治療と補液を行い回復した。登録症例は現在、経過を観察中である。BNCTを行った4例の腫瘍に対する平均線量は14.5～26.8Gy-eqであり、平均すると20.0Gy-eqであった。右肺が患側の場合、右肺に次いで、肝臓が第2の決定臓器となる。右肺が患側の症例は2件あったが、肝臓に対する線量は、最大18.1および18.5Gy-eq、平均5.5Gy-eqおよび4.9Gy-eqと評価された。

2．血清 VEGF 値は非中皮腫アスベスト関連疾患よりも有意に高く(Fig.1A)、病期の進行につれて増加する傾向が見られた(Fig.1B)。VEGF が 400pg/ml 以上の症例はそれ以下の症例に比べて生存期間が有意に短かった。

血清 TRX レベルの高い(60ng/ml 以上)悪性胸膜中皮腫の予後は、TRX レベルの高くない MPM(60 ng/ml 未満)に比して、生存期間が有意に短く、予後が悪かった。

FBS 添加では中皮細胞（Met5A）は影響を受けないが、中皮腫細胞(MSTO-211H, NCIH-2052, NCIH-2051, NCIH-2452,

NCIH-28)は遊走の促進が認められる(Fig.7)。中皮腫細胞の増殖には、他の癌細胞の増殖と同様に、Platelet-derived growth factor (PDGF)が極めて重要な役割を果たしている。PDGF-D は、Urokinase plasminogen activator (uPA)によって細胞外で切断され、活性型であるPDGF-DDを形成する。uPAを阻害するUrinary Trypsin Inhibitorにより遊走が抑制され、外因性PDGF-Dの影響に関しては、中皮腫細胞の遊走は明らかに促進されている。

3．V_{20} を20%以下にすることが肺障害を減少させることが分かった。実験結果からは、アスベスト暴露が基礎にある中皮腫患者で放射線肺臓炎の発生頻度が高くなる事が示唆された。

4．肺腺癌ではこれまで Cancer stem cell のマーカーは不明であった、NR0B1 分子を発現する細胞が Cancer stem cell の性質を示すこと、NR0B1 分子と結合する PPARγ遺伝子の発現低下が悪性度の低下につながることを明らかにした。

5．BPAおよびBSHに対して高い特異性と親和性を持つ、抗BPA抗(2B10)および抗BSH (A9H3)を作製した。Mab固定化したプレートを用いるELISAシステムは、BPAおよびBSHの単独溶液および混合溶液の簡便濃度分析法として有効であることが確認された。2B10による組織免疫染色により、BPAは腫瘍組織内に選択的に集積することが明らかとなった。また、免疫細胞染色から、BPAは全ての癌細胞の細胞質および核内に分布することが判明した。A9H3に免疫染色では、切片内のBSHが染色工程の洗浄等によって溶出され、鮮明な画像が得られなかった。しかし、疎水性を持つBSH誘導体の検出には有効であった。

6．企業と加速器中性子の出口での強度（フルエンス率：n/cm^2/s）は京大原子炉の現在の強度の約1.8であり、5cm深部で生まれる熱中性子の強度は2倍になることが分かった。また、現状の遮蔽では全身の被曝線量が原子炉中性子照射よりもやや高くなることが分かった。ただし、その時の放射線の主成分はγ線であるので遮蔽に工夫を加えることによって解決できることも分かった。生物学的特性、すなわち RBE は平均で 2.4-2.5 となり、原子炉中性子よりもやや小さかった。中性子のエネルギースペクトルの良く対応する結果と考えられる。

7．多重即発 γ 線テレスコープシステムの有効性が確認された。エネルギーの異なる γ 線の発生分布に関する情報を利用することで、硼素 10 と中性子との反応分布が評価できる可能性が示された。従来の肝腫瘍 BNCT だけでなく、胸膜中皮腫 BNCT にも適用可能であることが確認された。動きや変形の大きい肺を対象としたBNCTにおいては、このシステムは有力な線量評価ツールになると考えられる。QA ファントムについても、ファントム材中に混ぜるリチウム 6 の濃度を変えることで、中高エネルギーの中性子の分布状況が評価できることが示された。95%に濃縮したリチウム6を水酸化リチウムとして10%程度水に混ぜることで、高エネルギー中性子のみによる線量分布を評価できることが確認された。

D．考察

初回のPETでは略全ての症例で集積比がBNCTの適応基準としたT/B≧2.25に達しなかった。先行した抗癌化学療法の影響が継続していた可能性がある。その後、2-3ヶ月後の再検査でT/B値が上昇、再検査が実施出来た4例で基準値に到達した。その意味でPETの抗癌化学療法に対する効果評価における有用性を示すものと考えられる。

加速器中性子の物理学的特性が原子炉中性子よりも優れていたのは、そのエネルギースペクトルが高い方にシフトしており、中性子の深部への到達性が良いことによると考えられる。深部へより効率よく到達し、そこで熱中性子に変換される。RBEが原子炉中性子よりもやや小さいのは斯うした中性子エネルギーの高速側へのシフトに因ると考えて、合理的な説明が可能である。もとより加速器でも原子炉でも取り出された中性子は広いエネルギースペクトルを持つが、他家の論文における中性子エネルギーとRBEの関係図を基に両中性子のRBEをシミュレーションすると、原子炉中性子で大きく、我々の加速器中性子で小さい結果となり、値の比例関係は実測値での関係と正確に符合した。一部にエネルギーの高い加速器中性子を用いることに対する反対論もあったが、それは科学的根拠に乏しいものであることが明らかになった。

ホウ素薬剤を特異的に認識する抗BPA抗体および抗BSH抗体を用いた免疫化学的なホウ素薬剤の分析法を開発により、細胞内の分布が薬剤の性質によって顕著に異なることが確認できた。結果は多くの研究者による予想と同じであったが、分布の相違を画像で示し得たのは、不要な論争に終止符を打つ意味で意義が大きい。

E．結論

中皮腫へのBNCT臨床試験研究が開始され、PETでのホウ素製剤の取り込みに関する特徴、特に抗癌化学療法とのタイミングも次第に判明してきた。これらを参考に今後の臨床試験研究が推進できる。

加速器中性子の物理学的、生物学的特性が明確になり、その臨床試験に向けて大きく前進できた。

BPAおよびBSHの濃度測定法は、多剤BNCTにおけるホウ素薬剤の個別濃度分析法として有効な測定法である。また、免疫染色法は両薬剤の体内分布に関して、より詳細な画像情報を与えた。 本研究で確立された成果は、今後、BNCTの基盤技術に進展すると期待される。

F．研究発表

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G. 知的所有権の取得状況
1. 特許取得
なし
2. 実用新案登録
なし
3. その他
なし

研究成果の刊行に関する一覧表

雑誌

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Phase I Dose-escalation and Pharmacokinetic Trial of Lapatinib (GW572016), a Selective Oral Dual Inhibitor of ErbB-1 and -2 Tyrosine Kinases, in Japanese Patients with Solid Tumors

Kazuhiko Nakagawa[1], Hironobu Minami[2,†], Masayuki Kanezaki[3], Akihira Mukaiyama[3], Yoshiyuki Minamide[3], Hisao Uejima[1], Takayasu Kurata[1], Toshiji Nogami[1], Kenji Kawada[2], Hirofumi Mukai[2], Yasutsuna Sasaki[4] and Masahiro Fukuoka[1]

[1]Kinki University School of Medicine, Osaka, [2]National Cancer Center Hospital East, Chiba, [3]GlaxoSmithKline, Tokyo and [4]Saitama Medical School, Saitama, Japan

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Objective: The Phase I dose-escalation study was conducted to evaluate the safety and pharmacokinetics of lapatinib (GW572016), a dual ErbB-1 and -2 inhibitor, in Japanese patients with solid tumors that generally express ErbB-1 and/or overexpress ErbB-2.
Methods: Patients received oral lapatinib once daily until disease progression or in an event of unacceptable toxicity.
Results: Twenty-four patients received lapatinib at dose levels of 900, 1200, 1600 and 1800 mg/day; six subjects enrolled to each dose level. The majority of drug-related adverse events was mild (Grade 1–2); the most common events were diarrhea (16 of 24; 67%), rash (13 of 24; 54%) and dry skin (8 of 24; 33%). No Grade 4 adverse event was observed. There were four Grade 3 drug-related adverse events in three patients (i.e. two events of diarrhea at 1600 and 1800 mg/day each and γ-glutamyl transpeptidase increase at 1800 mg/day). The maximum tolerated dose was 1800 mg/day. The pharmacokinetic profile of lapatinib in Japanese patients was comparable to that of western subjects.
Conclusions: Lapatinib was well tolerated at doses of 900–1600 mg/day in Japanese solid tumor patients. Overall, our findings were similar to those of overseas studies.

Key words: ErbB-1 – ErbB-2 – lapatinib – phase I – tyrosine kinase inhibitor

INTRODUCTION

Dysregulation of the human epidermal growth factor (ErbB) family of cell surface receptors has been noted in several solid tumors. Binding of extracellular ligand to ErbB receptors activates multiple intracellular signaling pathways that can promote tumor growth through processes, such as cell proliferation, differentiation and inhibition of apoptosis. ErbB-1 and ErbB-2 are implicated in the pathogenesis of several cancers (1), and their overexpression in epithelial tumors—including those of the lung, breast, head and neck, colon, stomach, ovary and prostate—often correlates with poor prognosis (2,3).

ErbB receptors present two rational targets for inhibition: blockade of the extracellular ligand-binding domain by monoclonal antibodies and inhibition of the intracellular tyrosine kinase domain by small molecules (4). Several anticancer agents target specific ErbB isoforms. For example, the small molecule tyrosine kinase inhibitors gefitinib (Iressa®) and erlotinib (Tarceva®) and the monoclonal antibody cetuximab (Erbitux®) all target ErbB-1 (5–7), and thus, they are indicated for the treatment of non-small cell lung cancer (NSCLC) and colorectal cancer (8,9). Furthermore, a monoclonal antibody directed against ErbB-2 (trastuzumab, Herceptin®) has been approved for patients with ErbB-2-overexpressing breast cancer (10). Sensitivity to some of these agents is strongly associated with the expression levels of ErbB-1 and -2 (2,3).

For reprints and all correspondence: Kazuhiko Nakagawa, Kinki University School of Medicine, 377-2 Ohnohigashi, Osakasayama, Osaka 589-0014, Japan. E-mail: nakagawa@med.kindai.ac.jp

[†]Present address: Kobe University Hospital and Graduate School of Medicine, Hyogo, Japan

Since it has been suggested that tumors with ErbB-1 expression and ErbB-2 overexpression are more aggressive than those without expression of the receptors (11–13), it has been proposed that dual inhibition of ErbB-1 and -2 could be a useful approach in patients with overexpression of these receptors. Lapatinib (GW572016) is a potent, orally active, small molecule dual inhibitor of ErbB-1 and -2. Lapatinib markedly reduces autophosphorylation of ErbB-1 and -2, and inhibits activation of Erk1/2 and AKT, the downstream effectors of cell proliferation and cell survival, respectively (14–17). Lapatinib inhibits tumor cell proliferation in various human tumor cell lines expressing ErbB-1 and overexpressing ErbB-2, as well as in tumor xenograft models (14–17).

Preclinical study of lapatinib revealed the agent to be well tolerated with an effective half-life of ~24 h, suggesting once-daily oral administration to be feasible (18). Clinical studies of the safety and efficacy of lapatinib in cancer patients are underway.

This was the first Japanese Phase I study of lapatinib in patients with solid tumors. This study was primarily designed to assess the safety of repeated oral doses of lapatinib in these patients and to investigate pharmacokinetics to see if they are comparable with those in western patients.

PATIENTS AND METHODS

Study Design

This was a non-randomized, open-label, multicenter, dose-escalation Phase I study conducted at two sites in Japan—Kinki University Hospital, Osaka and National Cancer Center Hospital East, Chiba.

The primary objectives were to assess the safety of repeated oral doses of lapatinib, to determine the maximum tolerated dose (MTD) in patients with solid tumors, to evaluate the pharmacokinetics (PK) of repeated oral doses of lapatinib and to compare the data from overseas studies and based on these data, to find the clinically recommended dose of lapatinib in Japanese patients enrolled in further studies.

Patient Eligibility

Adult patients aged 20–74 years with histologically or cytologically confirmed solid tumors that are generally known to express EGFR and/or overexpress ErbB-2 (including colorectal cancer, gastric cancer, NSCLC and breast cancer) were eligible for inclusion, provided that they had failed standard therapies or there were no other appropriate therapies available (19–40). Patients had to have normal function of major organs and adequate bone marrow, hepatic and renal functions defined as hemoglobin $\geq$9 g/dl, neutrophil count $\geq$1500/mm^3 and platelets $\geq$100 000/mm^3, AST and ALT $\leq$2.5 of upper limit of normal (ULN) and bilirubin $\leq$1.5 of ULN, and serum creatinine $\leq$1.5 of ULN, respectively. Left ventricular ejection fraction by echocardiography had to be $\geq$50% and in all patients an appropriate length of time since cessation of previous therapy was required (chemotherapy, radiotherapy, surgery or investigational products other than anticancer drugs, $\geq$4 weeks; nitrosourea compounds or mitomycin C, $\geq$6 weeks; biologic response modifiers or hormone therapy, $\geq$2 weeks). Patients were also to have an Eastern Cooperative Oncology Group performance status (PS) 0–2 and life expectancy $\geq$3 months after the start of lapatinib treatment.

Exclusion criteria were serious complications (Grade $\geq$3 according to the National Cancer Institute common toxicity criteria, NCI-CTC, version 2); pleural effusion, ascites and/or pericardial effusion requiring drainage by puncture, intracavital administration, or any other relevant treatment; systematic steroid use for $\geq$50 days or possible need for long-term use of systemic steroids; multiple active cancers; symptomatic brain metastases; malabsorption and/or total resection of the stomach or small intestine; corneal disorder; history of drug allergy; breast feeding; previous trastuzumab-induced impaired cardiac function; and previous acute pulmonary disorder or interstitial pneumonia induced by gefitinib.

All patients gave written informed consent before the start of study. The protocol was approved by the institutional review board of each study site. The study was conducted according to the World Medical Association Declaration of Helsinki (41) and Japanese good clinical practice guidelines (42).

Treatment

Based on the findings of overseas Phase I study (43), and in order to compare PK profiles with an overseas parallel Phase I study (44), patients were assigned to receive lapatinib 900, 1200 or 1600 mg/day for 21 consecutive days. Lapatinib was taken orally once daily with water after a light low-fat breakfast, except on Days 1 and 21 when it was administered in fasting state.

The dose levels started at 900 mg/day and increased to 1200 and 1600 mg/day, then increased by 200-mg increments until MTD was reached. MTD was defined as the dose at which dose-limiting toxicity (DLT), i.e. a drug-related adverse event of NCI-CTC Grade $\geq$3, occurred within 21 days after the initiation of dosage in two or more patients at each dose level with six subjects. When DLT was observed, the next dose for the patients was to be postponed, and could not restart until NCI-CTC grade became $\leq$2 within 14 days. In such cases, when NCI-CTC became Grade 2 or below, the dose was to be restarted at the previous dose level. When NCI-CTC did not reach Grade 2 or below after dose delays of 14 days, the treatment for the patients was to be discontinued. These dose delays and reductions were allowed to be performed only once.

Although appropriate supportive care and symptomatic treatment were allowed, prophylactic use (including

antiemetics) was not permitted between screening and Day 21 of the treatment period. Anticancer therapy of any kind, medications that may affect the absorption or metabolism of lapatinib, and other investigational drugs were prohibited throughout the study. Also, to prevent PK interactions, patients were instructed to avoid grapefruit, grapefruit juice and St John's Wort (*Hypericum perforatum*) throughout the study.

Safety Assessments

Assessments including clinical laboratory tests, vital signs, PS and body weight were performed at screening, at baseline (i.e. within 3 days before the first dose), on Days 7, 14 and 21, every 4 weeks thereafter, on cessation of treatment, and on the last day of observation (i.e. 28 days after the final dose or immediately before the start of next anticancer therapy). Chest X-ray, 12-lead electrocardiogram and echocardiography were performed at screening, once between Days 14 and 21, and on the last observation day. Toxicity was graded according to the NCI-CTC version 2.

Pharmacokinetic Analysis

For PK evaluation, 3-ml blood samples were collected at 1 h pre-dosing and at 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after dosing on Days 1 and 21 and at pre-dosing on Days 7 and 14. Urine samples were collected before dosing on Day 1 and 0–24 h after dosing on Days 1 and 21.

Serum concentrations of lapatinib were measured by liquid chromatography tandem mass spectrometry with a lower limit of quantitation of 1 ng/ml.

The calculated PK parameters were maximum serum concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma drug concentration–time curve from 0 to 24 h (AUC_{0-24}) and terminal half-life ($t_{1/2}$). Renal clearance was calculated from urine concentrations of lapatinib.

Efficacy Assessments

For efficacy assessment [i.e. tumor response as determined by X-ray, computed tomography (CT), magnetic resonance imaging (MRI) and/or other objective measurements according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (45)], evaluations were performed at screening (i.e. 4 weeks before the first dose of lapatinib), once during Days 14–21, every 4 weeks thereafter, and on the last day of observation. Target and non-target lesions were assessed in the same manner before and after dosing. Consistency of efficacy evaluation by the study investigators was assessed by extramural review committee.

RESULTS

Patients

Twenty-four patients were enrolled; all had received prior chemotherapy. Table 1 shows their baseline characteristics. The median age was 60 years (range, 37–73), and they had a median PS of 1. NSCLC was the main tumor type. Six patients at four dose levels, 900, 1200, 1600 and 1800 mg/day each, received lapatinib. Eight patients received lapatinib for >3 months and four for >6 months.

All patients completed the initial 21-day treatment period, although one of the patients had dose reduction (overall compliance, 90.5%) due to the onset of a Grade 3 drug-related adverse event (diarrhea) during this period. Four patients (three at 1200 mg dose level and one at 1600 mg dose level) withdrew from study due to disease progression and four (one each at 900 and 1600 mg dose level and two at 1800 mg dose level) were withdrawn at their own request. Mean durations of study treatment in the 900, 1200, 1600 and 1800 mg groups were 131, 68.2, 117 and 49.3 days, respectively. No patient withdrew due to adverse events.

Safety

All 24 patients were eligible for safety analysis. Table 2 lists the drug-related adverse events experienced by ≥20% of

Table 1. Baseline characteristics of patients

Characteristic	Dose (mg/day)				Total ($n = 24$)
	900 ($n = 6$)	1200 ($n = 6$)	1600 ($n = 6$)	1800 ($n = 6$)	
Sex					
Male	5	2	3	4	14
Female	1	4	3	2	10
Tumor type					
Non-small cell lung cancer	5	3	1	4	13
Adenocarcinoma	2	1	1	3	7
Squamous cell carcinoma	2	1	0	1	4
Other	1	1	0	0	2
Colorectal cancer	1	1	2	1	5
Breast cancer	0	0	2	0	2
Others	0	2	1	1	4
Performance status[a]					
0	2	1	2	3	8
1	4	5	3	3	15
2	0	0	1	0	1

[a]Eastern Cooperative Oncology Group performance status.