厚生労働科学研究費補助金

第３次対がん総合戦略研究事業

新しい薬物療法の導入とその最適化に関する研究

平成１９年度～２１年度　総合研究報告書

研究代表者　田村　友秀

平成２２（２０１０）年　３月

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研究代表者　　田村　友秀　　国立がんセンター中央病院　総合病棟部長

研究要旨
新しい薬物療法の最適化を目指した、バイオマーカー研究と薬剤感受性規定因子解析を行い、以下の成果を得た。（１）肺癌化学療法における CEC 値の意義を検討した。EGFR-TKI による急性肺障害の関連遺伝子多型を見出した。（２）乳癌発現解析より効果予測系を樹立した。（３）胃癌発現解析から新規癌遺伝子、予後関連遺伝子を同定した。（４）YB-1 は HER1/2/3 発現や EGFR-TKI 感受性に関与する。（５）EGFR の糖鎖修飾は EGFR-TKI 感受性に関わる。HER2 陽性乳癌の HER2 阻害剤耐性に *PIK3CA* 遺伝子変異が関わる。（７）ソラフェニブは KRAS 野生型肺癌細胞では B-RAF、KRAS 変異細胞では C-RAF を標的とする。（７）BCRP 導入による EGFR-TKI 感受性変化を検討した。（８）新規血管新生抑制物質エポキシシノール B およびアザスピレンを見出し作用機序を解析した。

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A．研究目的

分子標的治療薬を中心とした新しい薬物療法の最適化を目指す。具体的には、（１）臨床検体を用いた効果・毒性に関わるバイオマーカーの探索、（２）薬剤感受性／耐性規定因子の解析と新薬の最適化研究、を実施する。

B．研究方法

研究組織は、研究代表者の他、８名の分担研究者で構成される。研究方法の詳細は、Ｃ項および分担研究報告書に記載する。

（倫理面への配慮）
基礎研究においては、施設の倫理規定等に従って、動物実験は適正飼育を行い、苦痛を最小限に抑えるよう配慮する。臨床研究においては、ヘルシンキ宣言、臨床研究およびヒトゲノム・遺伝子解析研究に関する倫理指針に従い、IRB 承認、被験者の同意、個人情報の遵守を必須とした。

C．研究結果

Ⅰ．臨床検体を用いた、治療効果・予後に関するバイオマーカーの探索

（１）非小細胞肺癌患者の化学療法前後の circulating endothelial cell (CEC) 値の解析から、CEC 値による治療の個別化の可能性を示唆した。肺癌患者の DNA を用いて、EGFR-TKI による急性肺障害の疾患-対照関連解析を行い、発症の人種差に矛盾せず、機能的にも説明可能な発症関連遺伝子多型を見出した。

（２）乳癌検体の細胞周期プロファイリングにおいて CDK2/1 活性比の高値群が予後不良で、化学療法高感受性であることを示した。術前化学療法前の乳癌組織の遺伝子発現プロファイル解析から、関連 70 遺伝子で構成する高精度効果予測システムを作成した。新規乳癌幹細胞マーカーALDH1 陽性の乳がんは、ER 陰性、HER2 陽性、Ki67 陽性の形質を有して化学療法に抵抗性であり、化学療法

耐性マーカーとなる。

（３）胃癌検体のマイクロアレイ解析により新規癌遺伝子候補 SRPX2 遺伝子を同定した。SRPX2 蛋白は新規コンドロイチン硫酸プロテオグリカンで、FAK を介して細胞接着能・遊走能を亢進させ、新たな治療標的候補となりうる。また、生存期間に相関した遺伝子 PDCD6 と MYLIP について機能解析を行った。一方、化学療法効果予測因子として同定した遺伝子群は５番染色体上に集中していた。

（４）乳癌、卵巣癌検体において、YB-1 の核内局在は抗癌剤耐性および生存率低下に関与し、EGFR, HER2、ERαの発現と関連した。肺癌細胞では YB-1 阻害により EGFR, HER2, HER3、Met 発現低下と EGFR-TKI 感受性低下を認めた。NDRG1/Cap43 の発現は、神経芽腫検体において N-myc 増幅と逆相関して良好な予後を示し、膵癌でも血管新生や腫瘍増大に抑制的に働くが、子宮頸癌では血管新生や悪性度と関連した。

（５）VEGFRs-TKI や PKC 阻害剤などの分子標的薬の早期臨床試験において、治療前後の FDG-PET を評価し、その有用性を検討した。

II. 分子標的薬の感受性/耐性規定因子の解析と新しい分子標的薬の最適化研究

（６）スニチニブは、リンパ管内皮細胞の VEGF-C シグナル伝達を阻害し、増殖、遊走、管腔形成を阻害した。動物モデルにおいてリンパ管新生を阻害しリンパ節転移を抑制した。ボルテゾミブは、血管内皮細胞に対して血管新生阻害、アポトーシス誘導を示すことを確認し、メカニズムを明らかにした。フコシルトランスフェラーゼ遺伝子の発現調節による EGFR の糖鎖修飾が EGFR-TKI の感受性に関わることを示した。HER2 陽性乳癌細胞株において HER2 阻害薬への耐性に *PIK3CA* 遺伝子変異が関わることを示した。

（７）抗 EGFR 抗体および新規サバイビン発現阻害剤の放射線感受性増強効果を動物モデルで確認し、作用メカニズムについて解析した。ソラフェニブは KRAS 野生型肺癌細胞では B-RAF を、KRAS 変異肺癌細胞では C-RAF を標的として抗腫瘍効果を発揮していることを見出した。

（８）抗癌剤の薬物動態や耐性機序に深く関わるトランスポーター研究において、BCRP 導入で EGFR-TKI 高感受性細胞のみが耐性となるメカニズムを明らかにした。P-gp 発現が MEK-ERK-シグナル伝達系によって特異的に制御されることを示した。ABCB5 は、6 回膜貫通領域と ATP 結合領域を持つ 1257 アミノ酸の ABC 輸送体であることを示した。

（９）ケミカルバイオロジー研究手法を用い、新規血管新生抑制物質エポキシシノール B およびアザスピレンを見出し、その作用メカニズムを解明した。また、多くの癌細胞で高発現する C7orf24 遺伝子の発現調節機構を解析し、新たな治療標的としての可能性を示した。

D．考察

新たな薬物療法から最大限の効果を引き出すには、作用メカニズムの解明と Proof of principle の検証、効果・毒性の予測バイオマーカーの探索、感受性／耐性規定因子の解析、に基づく治療の最適化が不可欠といえる。このような科学的・論理的な薬剤開発には、基礎研究者と臨床研究者の密接な研究連携、たとえば臨床検体を用いたトランスレーショナルリサーチが重要であり、本研究の特徴といえる。

本研究によりもたらされる成果が、効果増強、治療個別化、新たな創薬など、薬物療法の最適化につながり、難治がんの治療成績の向上に貢献することを期待する。

E．結論

本研究で得られた、分子標的薬の効果毒性など薬力学的作用のメカニズム、規定因子の解明、予測システムの樹立は、予後・治療効果の予測バイオマーカーとして有望であり、個別化治療への応用も期待される。また、耐性機構の解明や新たな標的分子の探索は、は治療効果増強、創薬に向け重要な知見といえる。

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G．知的所有権の取得状況

1．特許取得

特許公開

- 中枢神経系原発悪性リンパ腫マーカーおよびその用途（特許公開 2007-185127）
- 脳腫瘍患者の予後を予測するための脳腫瘍マーカーおよびその用途（特許公開 2007-089547）
- 悪性脳腫瘍マーカー遺伝子およびその用途（特許公開 2007-082433）
- 胃癌高発現遺伝子特定による胃癌診断および創薬への利用（特許公開 2008-118915）
- 胃癌の判定方法（特許公開 2009-276153）
- 結合型糖鎖を利用した膵臓癌の診断方法（特許公開 2009-270996）
- 5 員複素環化合物を有効成分とする抗ガン剤および新規 5 員複素環化合物（特許公開 2009-256274）
- 抗癌剤の有効性予測方法（特許公開 2009-244147）
- 乳癌術前化学療法に対する感受性の判定方法（特許公開 2009-272501）

特許出願中

- ロタキサン化合物及び抗ガン剤（PCT/JP2009/005503　国外）
- 治療効果観察のためのバイオマーカー使用方法又はシステム（EP 09154964.2 国外）
- A method of predicting the effect of a drug (PCT/JP2010/051304)

2. 実用新案登録

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3. その他

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研究成果の刊行に関する一覧表

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	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
1	Ando, R., Makino, Y., Tamura, T., Yamamoto, N., Nishigaki, R., Kimura, T., Yokote, N., Yamamoto, H.	Simple and sensitive HPLC method for determination of amrubicin and amrubicinolin human plasma: application to a clinical pharmacokinetic study.	Biomed Chromatogr.	4 (3)	301-306	2010
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研究成果の刊行に関する一覧表

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