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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２２年度～２４年度　総合研究報告書

研究代表者　田村　友秀

平成２５（２０１３）年　３月

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総合研究報告書

新しい薬物療法の導入とその最適化に関する研究

研究代表者　　田村　友秀　　国立がん研究センター中央病院　呼吸器内科長

研究要旨
薬物療法の最適化を目指した、バイオマーカーおよび薬剤感受性規定因子研究を行い、以下の成果を得た。（１）EGFR チロシンキナーゼ阻害剤による薬剤性肺障害に関連する SNP を特定、機能解析を行った。（２）血管新生阻害作用をもつ薬剤投与における CEC モニターの意義を評価した。（３）乳癌検体を用いて、メチル化 DNA 検出や、化学療法効果予測因子の解析を実施した。（４）日本人胃癌の 4.1%（11 / 267 例）に FGFR2 遺伝子の増幅がみられ、予後不良であることを見出した。（５）KRAS 遺伝子変異はセツキシマブの ADCC 抑制によっても治療抵抗性に関与した。（６）EGFR-TKI など BCRP 阻害作用をもつ薬剤による抗癌剤耐性克服法を検討した。（７）低酸素誘導因子－１の活性化経路を遮断する化合物のスクリーニング系を確立した。

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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について、（１）臨床検体を用いた効果、毒性のバイオマーカーおよび規定因子の解析、（２）細胞株などを用いた基礎における薬剤感受性/耐性規定因子の解明により、治療の個別化・最適化を確立し、治療成績の飛躍的向上を狙う。

B．研究方法

本研究組織は、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する。

C．研究結果

（１）臨床検体を用いた効果、毒性の規定因子の解析

① EGFR チロシンキナーゼ阻害剤による薬剤性肺障害について、疾患・対照症例の DNA を用いて、候補遺伝子解析を実施し、候補 SNP を特定して特許申請を行った（特願 2010-130992）（H22～）。機能解析として、当該 SNP が、遺伝子発現に及ぼす影響を検討した。ABCB1 遺伝子の CDS 部分、プロモーター部分の direct sequence を実施した。

② 血管内皮障害作用をもつパクリタキセルの効果予測バイオマーカーとして、circulating endothelial cell （CEC）

の有用性が示唆されていた（J Thorac Oncol 2009）。Gemcitabine との比較により、CEC がパクリタキセルの効果予測マーカーとして有用であることを報告した（H22～23）。また、プラチナ製剤、パクリタキセル、ベバシズマブの併用において、CEC が同様の変動を示すことを見出した（H24）。

③ 乳がんにおける遺伝子のメチル化と薬剤感受性の評価のため、従来法より高感度な血清中メチル化 DNA 検出法（one-step methylation-specific PCR assay（OS-MSP 法））を開発し、評価を行った（Breast Cancer Res Treat 2012）（H23～24）。また、乳がんの生検検体を用いて網羅的遺伝子発現解析行い、パスウェイ解析などから、術前化学療法の効果を予測する免疫関連遺伝子を抽出した（H24）。

④ FGFR2 遺伝子の増幅がみられる細胞株は、FGFR 阻害剤の感受性が極めて高い事が知られている（Br J Cancer 2007）。手術検体を用いた検討から、日本人胃癌の 4.1%（11 / 267 例）に当該遺伝子の増幅がみられ、予後不良であることを見出した。診断法として、qPCR ベースの Copy number assay、または FISH 法のいずれにおいてもほぼ同様の結果が得られることを報告した（H23～24、Br J Cancer 2012）。

（2）細胞株などを用いた基礎における薬剤感受性/耐性規定因子の解明

⑤ KRAS 遺伝子変異は抗 EGFR 抗体セツキシマブの直接効果を阻害するのみならず、Antibody-Dependent Cell-Mediated Cytotoxicity（ADCC）を抑制することよっても治療抵抗性を示すことを示した。KRAS 変異がセツキシマブに抵抗性をしめすことから、抗腫瘍効果における ADCC の役割は否定的であったが、本研究により ADCC が抗腫瘍効果に一定の役割を果たしている可能性を示した（H22、Cancer Sci 2010）。

⑥ チロシンキナーゼ阻害剤であるゲフィチニブ、エルロチニブ、ソラフェニブは、ABC トランスポーターである BCRP、pGP の基質となり、特に BCRP の阻害作用を強く持つことを示した。BCRP の発現により、耐性を示す CPT-11 などの抗癌薬は、これらの薬との併用により、その耐性が解除されることを示した。またこの効果は、BCRP の SNP により差があることも証明した（H23～24）。新規 BCRP 阻害剤である YHO-13177 は、強い BCRP 阻害作用をもつ一方で、p-GP と MRP1 を阻害しない、選択的 BCRP 阻害や下ることを証明した（H23、Cancer Sci 2011）。

⑦ 新規にスクリーニングで見出した数種類の Pim-1 キナーゼ阻害剤（小分子化合物）から、誘導体展開を行い、Pim-1 キナーゼに対する IC50 が 3 nM の特異性の高い TPC-052 を得た。FLT3 の活性変異体である FLT3 internal tendem duplication（FLT3/ITD）をもつ急性骨髄性白血病では、その下流の Pim-1 が活性化しており、TPC-052 が特異的な増殖抑制効果を発揮した（H24）。低酸素誘導因子－1（HIF－1）の活性化経路を遮断する化合物をスクリーニングするアッセイ系を確立した。低酸素条件下で低分子化合物のスクリーニングを行い、cytorienin A（H22～23）、verucopeptin（H24）などのリード化合物を見出した。verucopeptin は、各種スペクトル解析と化学分解、および各種標品の合成研究から、絶対立体化学の決定に成功した（H24）。

D．考察

薬物療法では、臨床効果や毒性に大きな個体差が存在し、有効例でもいずれ耐性を生じる。最大限の効果を得るには、「適切な患者に適切な治療を」という薬物療法の最適化が必要である。　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、規定因子の解明は、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が期待される。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。

E．結論

EGFR チロシンキナーゼ阻害剤による薬剤性肺障害に関連する SNP を特定、機能解析を行った。血管新生阻害作用をもつ薬剤投与における CEC モニターの意義を評価した。乳癌検体を用いて、メ

チル化 DNA 検出や、化学療法効果予測因子の解析を実施した。日本人胃癌の 4.1% (11 / 267 例) に当該遺伝子の増幅がみられ、予後不良であることを見出した。KRAS 遺伝子変異はセツキシマブの ADCC 抑制によっても治療抵抗性に関与した。EGFR-TKI など BCRP 阻害作用をもつ薬剤による抗癌剤耐性克服法を検討した。低酸素誘導因子－1 の活性化経路を遮断する化合物のスクリーニング系を確立した。

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G．知的所有権の取得状況

1．特許取得

（予定を含む）

① ソラフェニブの効果予測方法、西尾和人他3名、特許公開2012-249633、2012年12月20日公開

② EML4-ALK融合遺伝子の好感度検出方法、西尾和人、外5名、特許公開2012-100628、2012年5月13日公開

2.実用新案登録

なし

3.その他

特になし

研究成果の刊行に関する一覧表

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研究成果の刊行に関する一覧表

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