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学 位 論 文 題 名

Impact of baseline sum of longest diameter in target lesions by RECIST on survival of patients with metastatic colorectal cancer

(化学療法施行大腸癌における RECIST 標的病変長径和の予後因子としての意義)

学位論文内容の要旨

[Background] In patients with metastatic colorectal cancer (mCRC), several prognostic factors such as performance status (PS), number of metastatic sites, carcinoembryonic antigen (CEA), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) has been reported. Recently, Köhne et al reported prognostic factors on the multivariate analysis, using databases of 3825 metastatic CRC (mCRC) patients enrolled in prospective trials. Four independent baseline prognostic parameters, performance status, WBC, ALP and number of metastatic sites were identified. However, the above independent variables never reflect tumor volume (TV), although patients with large TV tended to have short survival times. RECIST (Response Evaluation Criteria In Solid Tumor) was established for the purpose to uniform reporting of outcomes of clinical trials. Overall response rate has usually been adopted for primary endpoint of a phase II study, in which documentation of the Baseline Sum Longest Diameter of target lesions (BSLD) is mandatory. BSLD can be considered to represent TV. The objective of this study was to clarify the prognostic impact of BSLD in target lesions by RECIST in patients with mCRC.

[Method] The subject of this study were consecutive 103 patients with mCRC treated with LV-modulated 5-FU or irinotecan in combination with 5-FU as the first-line treatment between September 2002 and March 2005. The treatment schedules consisted of the following six types of regimens; (i)5-FU+*l*-LV (RPMI regimen): *l*-LV 500 mg/m^2 in a two-hour intravenous (IV) infusion with 5-FU 600 mg/m^2 as an IV bolus one hour after the *l*-LV had begun, given once every week for four weeks, and repeated every six weeks, (ii) UFT/LV: UFT 300 mg/m^2 and LV 75mg/body were orally administered daily for four weeks followed by one-week rest, and repeated every five weeks, (iii) Bolus 5-FU plus irinotecan (IFL): irinotecan 100 mg/m^2 as a 90-minute IV infusion, *l*-LV 10mg/m^2 as an IV bolus, and then 5-FU 500mg/m^2 as an IV bolus infusion, given once every week for 4 weeks, and repeated every 6 weeks, (iv) Infusional 5-FU plus irinotecan (FOLFIRI): *l*-LV 200mg/m^2 as a 2-hour IV infusion, irinotecan 180mg/m^2 as a 90-minute IV infusion followed by IV bolus 5-FU 400 mg/m^2, and a 46-hour infusion of 5-FU 2,400mg/m^2 given every other week. All patients routinely received 3 mg of granisetron plus 8 mg dexamethasone in a 30-minute IV infusion before administration of irinotecan. Treatment continued until disease progression, unacceptable toxicity, or patient refusal. Whenever severe adverse events occurred, the doses were adjusted to appropriate levels of tolerance based on the physician's assessment. Any grade 3 or 4 adverse event resulted in an approximately 20% dose reduction of bolus 5-FU for

subsequent cycles for RPMI and UFT/LV, 20% dose reduction of irinotecan and bolus 5-FU for IFL, 20% dose reduction of irinotecan and infusional 5-FU and 50% dose reduction of bolus 5-FU for FOLFIRI. Persistent grade 2 or worse adverse events delayed therapy until recovery. The use of colony-stimulating factors was allowed if medically justified. Intensive treatment with loperamide, if needed, was used for diarrhea. Other supportive treatments were given if required. The Kaplan–Meier method was used to evaluate median overall survival. The univariate and multivariate analyses of prognostic factors using a Cox proportional hazard model were carried out with categorized variables to calculate risks and their 95% confidence interval (95% CI). The factors with substantial impacts ($p<0.10$) in the univariate analysis were introduced to a Cox proportional hazard model in the multivariate analysis with backward selection. The following nineteen categories were examined: age; gender, ECOG PS; 0 or 1 versus 2, recurrence or unresectable, primary tumor resection; - versus +, tumor location; rectum versus colon, peritoneal dissemination; + versus -, pleural effusion (PE) and/or ascites; + versus -, number of metastatic sites; 1 versus > 1, treatment regimen: LV-modulated 5-FU regimen versus irinotecan containing regimen, WBC; ≥10,000 versus <10,000/mm^3, ALP; ≥300 versus <300IU, LDH; ≥300 versus <300IU, CEA; ≥5 versus <5ng/ml, liver metastasis; + versus -, BSLD (cm), BSLD; ≥5 versus <5cm, BSLD; ≥10 versus <10cm, BSLD; ≥median versus <median. The calculations were performed using the SAS Ver 8.02 (SAS Inc, USA).

[ResultsI In this study, median age was 62 years. Sixty-six percent of the patients had an ECOG PS of 0 at base line. Seventy-six percent of the patients had at least two organs involved, being the liver being the most common site of metastasis. The chemotherapy regimens included leucovorin-modulated 5-FU (n=27) and 5-FU plus irinotecan (n=76). The median overall survival time (MST) was 547 days. The median BSLD was 14.3 cm (range, 1.1-54.7). In univariate analysis, identified prognostic variables on survival were PS (0, 1 versus 2), number of metastatic sites (1 versus >1), peritoneal dissemination (+ versus -), pleural effusion (PE) or/and ascites, WBC (≥ versus < 10,000/mm^3) , ALP (≥ versus < 300 IU), LDH (≥ versus < 300 IU) , CEA (≥ versus < 5ng/ml), chemotherapy regimen, presence of liver metastasis, and BSLD. In multivariate analysis with covariates of the above significant factors, BSLD (≥ versus <10cm) (HR 0.431, 95%CI 0.237-0.785, p=0.0059), PS (HR 0.248, 95%CI 0.107-0.577, p=0.0012), PE and/or ascites (HR 0.402, 95%CI 0.228-0.708, p=0.0016) were independent prognostic factors.

[Discussion] Although we have experienced that patients with huge tumor volume would have poor prognosis and have used RECIST in many clinical trials, it is not clear whether baseline sum longest diameter of target lesion could be one of prognostic factors on overall survival in patients with unresectable or metastatic CRC. We retrospectively investigated the correlation of overall survival with clinical characteristics of patients who underwent the front-line chemotherapy at our institution. The univariate and subsequent multivariate analyses demonstrated that ECOG PS, PE and/or ascites, and BSLD (10cm) before the initial chemotherapy could be independent prognostic factors on overall survival. The ECOG PS had previously been reported as one of the prognostic factors in metastatic colorectal cancer patients in several studies. The results of the present study were compatible with those of the past studies. PE and/or ascites was the most significant variable while it was not in the previous reports. Although patients having PE and/or ascites are usually excluded from clinical trials, they were not excluded from the selection criteria in the present study because are routinely treated in clinical practice setting. The reason that PE and/or ascites could be the most significant variable might be derived from the difference of the patient population. And this study suggests that it may be reasonable that usual clinical trials exclude patients with PE and/or ascites. It is suggested that the BSLD (10cm) might be an independent prognostic factor. Because our findings were based on a retrospective analysis in the single institution, validation of the usefulness of baseline

sum longest diameter of target lesions is necessary and ongoing, using the other prospective cohorts.
[Conclusion] Baseline sum longest diameter of target lesions by RECIST representing tumor volume might be an independent prognostic factor of patients with mCRC after systemic chemotherapy.

学位論文審査の要旨

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2002 年ドイツのケーネらが転移性大腸がんを対象とした複数の臨床試験から集積された 3825 名を対象に予後因子解析を行った結果，白血球数，ALP，転移臓器個数，PS が予後因子とされた。この 4 つのをパラメータとして high，intermediate，low の 3 つのリスクグループに分けるケーネインデックスが作成され，別コホートで検証も行われた信頼たる予後因子モデルとされている。しかし腫瘍量を反映する変数はこのモデルの解析には含まれていない。そこで抗がん剤の効果判定に用いられている RECIST の治療前の標的病変の長径和(Baseline Sum of Longest Diameter : BSLD)が腫瘍量を表現できるものと考え，BSLD が予後因子となるかを明らかにすることにした。

対象は 2002 年 9 月から 2005 年 3 月までに静岡がんセンターにて初回化学療法を施行された大腸がん患者 103 例で，治療レジメンは 5-FU ベースの 5-FU+LV と UFT/LV 療法，5-FU+イリノテカンの治療としては 5-FU が急速静注投与の IFL 療法と持続静注投与の FOLFIRI 療法が施行された。

患者は年齢中央値が 62 歳，男 63 例，女 40 例，PS0 ないし 1 がほとんどであった。胸腹水をともなうものが全体の 3 割で，BSLD の中央値は 14.3cm であった。ケーネインデックスでは high が約半数を占めており全体的に予後不良な対象と考えられた。単変量解析の結果では PS,転移臓器個数，白血球数，ALP そしてケーネインデックスそのものが有意な結果であり，また腹膜播種，胸腹水，治療レジメン，LDH，CEA，肝転移の有無も有意な結果であった。また BSLD については連続量，5cm，10cm，中央値のすべてが有意な結果であったが 10cm が一番ハザードが大きかったため多変量解析に組み入れることにした. 多変量解析では PS，胸腹水の有無，BSLD(10cm)が有意な予後因子となった。

予後因子解析は臨床試験参加患者に対し行われることが多いため胸水や腹水が予後因子となることは過去に報告はないが胸腹水も含まれる対象であったため予後因子となったと思われた。PS については過去に報告も多く矛盾のない結果と思われた。今回の目的であった BSLD も予後因子であることが示唆されたが，単施設の後向き研究であり今後は検証が必要と考えられた。

公開発表では学位論文内容の発表の後，副査近藤哲教授よりケーネの研究の中で腫瘍量を表現したものがあったのか，CEA の値はどうなのか，治療経過中の外科手術は検討されたのかの質問があった。申請者は一つ目の質問に対しては画像での腫瘍量の表現はなく，検査値データとしての CEA, LDH については必ずしも上昇するパラメータではないと述べた。また二つ目の質問については予後因子解析はあくまで治療前の背景因子が対象となるので経過中の治療については検討していないと述べた。次いで副査浅香正博教授から RECIST 作成当時の治療の時代背景の確認の質問がなされた。申請者はこれに対しイリノテカン治療も標準治療には至っておらず，5-FU が標準治療であったと述べた。また浅香教授から肺転移の予後については悪そうだが予後因子にならないのかと質問があったが，申請者は大腸癌の肺転移は他の消化器癌と異なり局所治療が有効で切除可能な場合 5 年生存率が 30%を超えるなど，必ずしも悪い状況ともいえないので今回予後因子とならなかった結果は妥当だと述べた。ついで主査である秋田弘俊教授から大腸癌において以前に同じような研究はあるのか，また大腸癌以外での同様の報告はあるのかと質問がなされた。それに対し申請者は現在も大腸がんにおいては同様の報告はないこと，大腸癌以外では申請者の研究施設での胃癌症例でも同様の結果であったと述べた。さらに秋田教授から発表内で前向きな検証を行っているとされた点についての追加説明の要望があった。申請者はこれに対し，企業の治験のデータを解析予定と述べた。さらに秋田教授から，この予後因子についての今後の見通し，社会的有用性について質問がなされたが，申請者はケーネが施行したような大規模な予後因子解析で実証された際には，今後の第二相試験の結果報告の際には背景因子として BSLD を報告し各臨床試験背景として比較できるようになること，さらには第三相試験の前層別因子の候補とすることも想定していると述べた。本研究は転移性大腸癌において腫瘍量が予後不良因子であることを初めて示唆したことで高く評価され，今後さらに検証が進み臨床試験への取り込みが行われることが期待される。

審査員一同は，これらの成果を高く評価し，大学院課程における研鑽や取得単位なども併せ申請者が博士（医学）の学位を受けるのに充分な資格を有するものと判定した。