<<　キャプテム（cap/tem）概要　>>

近年、抗がん剤であるカペシタビンとテモダールを併用した NET の臨床試験が進んでいます。
日本ではまだ未認可ですが、外国での治験の進捗状況によって日本でも認可されることを期待します。

【例－１】臨床試験（第２相）の報告例

題目：　Capecitabine plus temozolomide (CAP-TEM) in patients with advanced neuroendocrine neoplasms (NEN): An Italian multicenter retrospective analysis.

文献名：　J Clin Oncol 32, 2014 (suppl 3; abstr 281)

研究者名：　Francesca Spada, 他　Italy

要旨：

Background: A combination of capecitabine (CAP) and temozolomide (TEM)has been successfully used as first-line treatment in low-grade pancreatic neuroendocrine neoplasms (PNEN). We reviewed activity and toxicity of the same regimen in patients with advanced NEN with different primary and grading.

Methods: Clinical data of patients who had received oral CAP 1500 mg/m2/day over 14 days bid plus oral TEM 150-200 mg/m2/day on days 10-14 of each 28-day cycle, were retrospectively reviewed. The methylenguanilmetiltransferase (MGMT) methylation-status (MGMT-gene >5% = responders) and TS-polymorphisms (2R/2R, 2R/3R = responders, 3R/3R = non-responders) in tumor-tissue/peripheral-blood were evaluated by pyrosequencing.

Results: Since March 2012, 29 patients were selected. The primary tumor was: pancreas in 14 patients (48%), gastrointestinal (GI) in 5 (17%), unknown in 2 (7%), lung in 8 (28%). According to 2010 WHO classification, Ki67 was <2% (G1) in 3%, 3-20% (G2) in 45% patients, >20% (G3) in 21% with two "low G3" (Ki67 21-30%), and unknown in 3%. Among lung: 7% typical and 21% atypical (Travis' classification). 72% patients (21/29) were progressive on different therapies: peptide-receptor-radiotherapy (38%), chemotherapy (38%), everolimus (14%). Partial-response (PR) occurred in 14% (4/29) of patients (95% CI: 4-32), stable-disease (SD) in 59% (17/29) (95% CI: 39-77) mainly PNET. The two "low G3" responded. Disease control rate (PR+SD): 72% (95% CI: 53-87). Median TTP: 9 months (95% CI: 5.6-N.E.). Thrombocytopenia was the most frequent grade 3 toxicity, always temporary. All 4 PR patients had genotype 2R/3R-2R/2R investigated for the 28 base-pair (bp) variable number of tandem repeats (VNTR) in the 5'UTR of the TS-gene, and MGMT-gene inactivation by epigenetic silencing.

Conclusions: This analysis suggests that CAP-TEM chemotherapy could be active and well tolerated in pretreated patients with advanced NEN of different origins and grading. This warrants a prospective investigation in a more homogeneous population (G2 and "low-G3" GEP NEN or lung carcinoids), in order to validate the predictive value of MGMT methylation-status and TS-polymorphisms.

【例－２】臨床試験（第２相）の報告例

題目：Capecitabine and temozolomide (CAPTEM) for metastatic, well-differentiated neuroendocrine cancers: The Pancreas Center at Columbia University experience

文献名：　Cancer Chemotherapy and Pharmacology (2013), 71(3), 663-670.

研究者名：y: Fine, Robert L. 他（アメリカ）

要旨：

Purpose: We evaluated the efficacy and safety of capecitabine and temozolomide (CAPTEM) in patients with metastatic neuroendocrine tumors (NETs) to the liver. This regimen was based on our studies with carcinoid cell lines that showed synergistic cytotoxicity with sequence-specific dosing of 5-fluorouracil preceding temozolomide (TMZ).

Methods: A retrospective review was conducted of 18 patients with NETs metastatic to the liver who had failed 60 mg/mo of Sandostatin LAR® (100 %), chemotherapy (61 %), and hepatic chemoembolization (50 %). Patients received capecitabine at 600 mg/m^2 orally twice daily on days 1-14 (max. 1,000 mg orally twice daily) and TMZ 150-200 mg/m^2 divided into two doses daily on days 10-14 of a 28-day cycle. Imaging was performed every 2 cycles, and serum tumor markers were measured every cycle.

Results: Using RECIST parameters, 1 patient (5.5 %) with midgut carcinoid achieved a surgically proven complete pathol. response (CR), 10 patients (55.5 %) achieved a partial response (PR), and 4 patients (22.2 %) had stable disease (SD). Total response rate was 61 %, and clin. benefit (responders and SD) was 83.2 %. Of four carcinoid cases treated with CAPTEM, there was 1 CR, 1 PR, 1 SD, and 1 progressive disease. Median progression-free survival was 14.0 mo (11.3-18.0 mo). Median overall survival from diagnosis of liver metastases was 83 mo (28-140 mo). The only grade 3 toxicity was thrombocytopenia (11 %). There were no grade 4 toxicities, hospitalizations, opportunistic infections, febrile neutropenias, or deaths.

Conclusions: CAPTEM is highly active, well tolerated and may prolong survival in patients with well-differentiated, metastatic NET who have progressed on previous therapies.

PanCan-Japan ホームページより：

ロバート・L・ファイン氏は、サンフランシスコ、カリフォルニア州で開催された ASCO GI において、神経内分泌腫瘍の様々なタイプの患者を対象とした「テモゾロミド＋カペシタビン（CAPTEM）」併用療法の第 II 相臨床試験結果を発表した。膵神経内分泌腫瘍、消化管神経内分泌腫瘍/カルチノイド（様々な原発巣）、および神経内分泌腫瘍の他のタイプのある 28 人の患者が参加した臨床試験であった。無増悪生存期間中央値（PFS）は、ほぼ 2 年に達したなか、患者の 11％で完全奏功（CR）、32 ％で部分奏功（PR）、54 ％で安定（SD）がみられたとファイン氏が報告した。

【例－３】アメリカ国立がんセンターでの治験例（第２相試験：抜粋）：

題目：　Capecitabine and Temozolomide for Neuroendocrine Cancers

要旨： This phase II study is designed to assess whether treatment with capecitabine/temozolomide (CAP/TEM) is safe and effective in treating subjects with progressive, differentiated, metastatic neuroendocrine tumors (NET). The primary objective of the study is to determine the radiologic response rate to this regimen in progressive, metastatic, differentiated neuroendocrine cancers. Secondary objectives include determining the overall and one year survival rates to this regimen, to determine progression free survival, to assess toxicities, improvement of quality of life, biochemical responses of tumor markers, and relief from NET symptoms.

今後の展望（抜粋）： In total, an estimated 12,000 - 15,000 cases of NETs (not counting small cell carcinomas) are diagnosed in the United States annually. The incidence of carcinoid tumors alone is estimated to be 2 per 100,000 in the United States (5,400 cases/yr/U.S.). PETs are less common, with about 1,000 new cases per year in the United States. Carcinoids and PETs are potentially curable by surgical resection; the 5-year survival rates in patients with localized carcinoid is 78.2%. However, these tumors are frequently indolent in their growth and patients often present with unresectable or metastatic disease (80% of all cases). The hormonal symptoms that may accompany their disease, as exemplified by carcinoid syndrome, complicate the management of these patients. Hormonal therapy, namely octreotide, is used to relieve symptoms and has been reported to have a response rate of 1-5% by itself. Metastatic disease is associated with significantly worse prognosis; carcinoid patients with visceral metastases have a 5-year survival rate of 38.5%. Based on the efficacy of the combination of cisplatin and etoposide in treating small cell lung cancer, these agents have been explored in the treatment of pancreatic islet cell tumors and carcinoids. In general, etoposide-cisplatin regimens have poor response rates for the slow growing, differentiated NET group with an average response rate of 7-10%. Furthermore, these cisplatin-etoposide regimens have been associated with significant toxicities, including frequent severe neutropenia, ototoxicity, neurotoxicity and nephrotoxicity.

An Eastern Cooperative Oncology Group (ECOG) trial of patients with metastatic or unresectable progressive pancreatic islet cell tumors, including poorly and well-differentiated PETs, showed that a regimen of streptozocin and doxorubicin had a significantly superior objective response rate compared to a combination of streptozocin and fluorouracil (69 versus 45%, p=0.05). The study used a definition for objective response that included regression of the tumor mass, regression of malignant tumor causing hepatomegaly or a reduction in excessive hormone production. Streptozocin-doxorubicin was also significantly superior to streptozocin-fluorouracil in terms of median time to tumor progression and of median overall survival (2.2 versus 1.4 years, p=0.004). However, significant toxicity was associated with either streptozocin-based regimen with roughly 80% in either arm experiencing vomiting that lasted throughout the 5-day course of streptozocin per cycle. Additionally, Grade 3/4 leukopenia occurred in 25% of patients who received streptozocin-fluorouracil, with one treatment-related death secondary to leukopenia complicated by

sepsis. Notably, streptozocin has significant renal toxicity causing significant proteinuria. Thus, the doubtful efficacy of streptozocin-based combinations and the significant associated toxicity has limited the role of cytotoxic chemotherapy in the treatment of differentiated NETs.

In our lab, we have found that capecitabine (5-DFUR), an oral pro-drug for 5-FU, and temozolomide were synergistic for induction of apoptosis in 2 human NET cell lines. The mechanism and pathways involved are under investigation, but we found it was important for the synergism that temozolomide be exposed to the NET cell lines during the end of the capecitabine exposure. We believe that the combination of temozolomide and capecitabine will prove to be an effective regimen. Our hypothesis is that the DNA damage induced by capecitabine by incorporation of 5-FdUTP into DNA and reducing thymidine pools by inhibition of thymidylate synthase via 5-FdUMP will synergistically potentiate the effect of temozolomide as an alkylator by reducing the repair activity of O6-alkylguanyl-alkyl-transferase (O6-AGAT). O6-AGAT is a DNA repair enzyme which removes temozolomide-alkylated groups from guanine. A 5-day regimen of temozolomide is vital to decreasing O6-AGAT levels by direct binding which leads to a suicide inactivation of O6-AGAT-mediated DNA repair. This saturates O6-AGAT after 23 days of temozolomide, thus allowing the last 23 days of dosing to induce alkylation of DNA and thereby induce apoptosis. We found that cells with prior 5-FU exposure were more sensitive to the induction of apoptosis by temozolomide.

Another fundamental rationale and hypothesis which we have developed into the synthesis of a novel regimen for NET is based upon cytokinetics and p53. NET are characteristically very slow growing, yet fatal, cancers with the great majority of them having wild type p53. Therefore, their drug resistance is probably not based upon mutational p53 causes because of the wild type p53 status but rather upon their slow cytokinetics. The best way to kill slow growing tumors with a long interval in G0 phase is with lipophilic alkylators (i.e. Temodar) and utilizing continuous exposure to antimetabolites such as Xeloda or continuous infusion 5-FU. Xeloda's half-life is 11 hrs so q 12 hr dosing is roughly equivalent to continuous infusion. We believe our hypothesis is correct and well grounded in pharmacologic and cell cycle principles.

We have to date pilot experience of ten patients who received capecitabine, total of 1500 mg/m2/day/PO, for fourteen days, with temozolomide 150-200 mg/m2 given on the last five days of their course of capecitabine. All of our initial 10 patients with progressive, differentiated NET have had dramatic symptomatic pain relief and at least 75% reduction in their tumor markers. Five patients had metastatic carcinoid and 5 had metastatic pancreatic NET. All patients had progressive liver metastases, all 10 patients had failed octreotide therapy with long acting somatostatin, and 7/10 had failed prior chemotherapy regimens. One carcinoid patient had a complete response (CR) proven by surgery and is now without any tumor recurrence 22 months out from surgery and chemotherapy. Three patients had a partial response (PR) and one patient had a minor response (MR) in their liver metastases. Two other patients experienced stable disease (SD) for 6 and 8 months while on therapy. The overall response rate proven by CT or MRI scans (CR, PR and MR) is 50% to date. Overall, clinical benefit of this lab based regimen occurred in 7/10 patients (CR, PR, MR

and SD). Toxicities have all been minor with none over grade 2 myelosuppression. There were no hospitalizations or complications or side effects except grade 12 nausea during temozolomide therapy. Therefore, we wish to begin a formal protocol evaluating the role of these two drugs in this disease.