〔 論文・著書 〕

＜神経筋疾患＞

1. Clonic perseveration in the subacute stage of Japanese encephalitis

Ono Y, Manabe Y, Sakai K, Hayashi Y, Abe K

J Neurol Sci 251(1-2), 107-109, 2006 Dec. Epub 2006 Nov 9.

We report a very rare case of Japanese encephalitis (JE) presenting with reversible stereotyped movement in the subacute stage. A 58-year-old woman presented with high fever, headache, nausea, vomiting, and consciousness disturbance. Cranial magnetic resonance imaging (MRI) of fluid attenuated inversion recovery (FLAIR) and T2-weighted image (WI) showed high intensity areas in the bilateral thalamus, caudate nucleus and hippocampus. She developed coma, convulsion, and ballism in the acute stage. One month after onset, she showed rhythmic, stereotyped, repetitive movements with hypoperfusion in the thalamus and frontal cortex on single photon emission computed tomography (SPECT). Three months later, her stereotyped movement improved accompanied by recovery of hypoperfusion in the thalamus and frontal cortex on SPECT. We speculated that her stereotyped movement was clonic perseveration due to frontal dysfunction induced by thalamofrontal disconnection.

2. Protein-bound crotonaldehyde accumulates in the spinal cord of superoxide dismutase-1 mutation-associated familial amyotrophic lateral sclerosis and its transgenic mouse model

Shibata N, Kawaguchi M, Uchida K, Akiyoshi K, Hitoshi T, Nakano R, Fujimura H, Sakoda S, Ihara Y, Nobukuni K, Takehisa Y, Kuroda S, Kokubo Y, Kuzuhara S, Honma T, Mochizuki Y, Mizutani T, Yamada S, Toi S, Sasaki S, Iwata M, Hirano A, Yamamoto T, Kato Y, Sawada T and Kobayashi M

Neuropathology 27(1) 49-61, 2007

Growing evidence documents oxidative stress involvement in ALS. We previously demonstrated accumulation of a protein-bound form of the highly toxic lipid peroxidation product crotonaldehyde (CRA) in the spinal cord of sporadic ALS patients. In the present study, to the determine the role for CRA in the disease processes of superoxide dismutase-1 (SOD1) mutation-associated familial ALS (FALS), we performed immunohistochemical and semi-quantitative cell count analyses of protein-bound CRA (P-CRA) in the spinal cord of SOD1-mutated FALS and its transgenic mouse model. Immunohistochemical analysis revealed increased P-CRA immunoreactivity in the spinal cord of the FALS patients and the transgenic mice compared to their respective controls. In the FALS patients, P-CRA immunoreactivity was localized in almost all of the chromatolytic motor neurons, neurofilamentous conglomerates, spheroids, cordlike swollen axons, reactive astrocytes and microglia, and the surrounding neuropil in the affected areas represented by the anterior horns. In the transgenic mice, P-CRA immunoreactivity was localized in only a few ventral horn glia in the presymptomatic stage, in almost all of the vacuolated motor neurons and cordlike swollen axons and some of the ventral horn reactive astrocytes and microglia in the onset stage, and in many of the ventral horn reactive astrocytes and microglia in the advanced stage. Cell count analysis

on mouse spinal cord sections disclosed a statistically significant increase in the density of P-CRA-immunoreactive glia in the ventral horns of the young to old G93A mice compared to the age-matched control mice. The present results indicate that enhanced CRA formation occurs in motor neurons and reactive glia in the spinal cord of SOD1-mutated FALS and its transgenic mouse model as well as sporadic ALS, sug- gesting implications for CRA in the pathomechanism common to these forms of ALS.

3. **Frequency and clinicopathological characteristics of alcoholic cerebellar degeneration in Japan: a cross-sectional study of 1,509 postmortems**

Yokota O, Tsuchiya K, Terada S, Oshima K, Ishizu H, Matsushita M, Kuroda S, Akiyama H

Acta Neuropathol (Berl) 112(1), 43-51, 2006. Epub 2006 Apr 19.

Alcoholic cerebellar degeneration (ACD) is a pivotal neurological complication in alcoholics. However, although there are a few autopsy reports and some data on its frequency, it is considered very rare in Japan. The aims of this study were (1) to estimate the frequency of the disease in Japanese autopsy cases, and (2) to examine the clinicopathological features of symptomatic and asymptomatic cases of ACD. We reviewed the records of 1,509 Japanese autopsies obtained from three autopsy series in Japan, and selected all 55 cases (3.6%) with alcoholism. On neuropathological reexamination, ACD was confirmed in six male alcoholics [0.4% of all subjects; 10.9% of all alcoholics; mean age at death 59.3+/-13.4 years (+/- SD)], including three asymptomatic cases. These frequencies were much lower than some previous Western findings, but more common than that has been expected in Japan. The frequencies of memory impairment and ataxia in ACD cases were significantly higher than those in alcoholics without any alcohol-related pathologies. In ACD cases, loss of Purkinje cells, narrowing of the width of the molecular layer, and tissue rarefaction in the granular layer were observed in the anterior and superior portions of the vermis of the cerebellum. In adjacent regions, the Purkinje cell and molecular layers were more mildly affected. The distribution of severely affected regions was more restricted in the asymptomatic cases than in the symptomatic cases. This study confirmed the frequency of asymptomatic cerebellar degeneration in alcoholics, suggesting that early intervention in alcoholism in the subclinical phase is important to prevent the development of cerebellar symptoms.

4. **Lewy body variant of Alzheimer's disease or cerebral type lewy body disease? Two autopsy cases of presenile onset with minimal involvement of the brainstem.**

Yokota O, Tsuchiya K, Uchihara T, Ujike H, Terada S, Takahashi M, Kimura Y, Ishizu H, Akiyama H, Kuroda S

Neuropathology 27(1), 21-35, 2007.02

Lewy bodies (LB) usually extend from the brainstem to the cerebrum in patients with Parkinson's disease. However, whether the patterns of progression of LB and neuronal loss in Parkinson's disease are identical to those in other Lewy body diseases (LBD) remains unclear. In addition, pathological data on the autonomic nervous system involvement in LBD are limited. We present here the clinicopathological

characteristics of two autopsy cases with both Alzheimer's disease and dementia with Lewy bodies (DLB), possibly diagnosed as having Lewy body variant of Alzheimer's disease (LBV/AD). Our patients presented clinically with dementia without parkinsonism. Histopathologically, phosphorylated alpha- synuclein-positive LB and Lewy neurites were abundant in the limbic system, especially in the amygdala, and to a lesser degree, in the neocortex, including the primary motor cortex. The amygdala was also most severely affected by neuronal loss, and the other limbic areas and neocortex were affected to a lesser degree. Despite the existence of a small number of LB and many Lewy neurites, neurons in the brainstem nuclei were relatively well preserved. The Braak stages of concurrent neurofibrillary changes and senile plaques were stage V and C, respectively, in both cases. Tyrosine hydroxylase-positive nerve fibers were relatively well spared in one case examined compared with Parkinson's disease cases. Furthermore, many Lewy neurites immunopositive for phosphorylated a-synuclein were found in the nerve fascicles of the epicardium in one case examined and in Parkinson's disease cases to a lesser degree. These findings suggest that: (i) in at least some LBV/AD cases, the amygdala develops neuronal loss and Lewy-related pathology prior to the brainstem nuclei; and (ii) the depletion of nerves in the heart tissue of LBV/AD is not necessarily complete despite the development of Lewy-related pathology.

5. Effects of group-home care on behavioral symptoms, quality of life, and psychotropic drug use in patients with frontotemporal dementia.

Yokota O, Fujisawa Y, Takahashi J, Terada S, Ishihara T, Nakashima H, Oshima E, Kugo A, Ata T, Ishizu H, Kuroda S, Sasaki K

J Am Med Dir Assoc 7(5), 335-337, 2006

6. Quality of life for patients with schizophrenia in a Japanese psychiatric hopital

Kugo A, Terada S, Ishizu H, Takeda T, Sato S, Habara T, Fujimoto Y, Namba T, Kuroda S

Psychiatry Res 144(1), 49-56, 2006. Epub 2006 Aug 21.

Providing a good quality of life (QOL) has recently been recognized as a central purpose of health care in psychiatry. In this study, we performed a detailed evaluation of the subjective QOL of schizophrenic inpatients and examined the relationship of QOL to various patient characteristics. This study was conducted on schizophrenic inpatients and nursing staff members in a Japanese private psychiatric hospital. As a result, only depression showed a weak, but significant, relationship with subjective QOL. Other characteristics showed no meaningful correlation to subjective QOL. Comparison between the schizophrenic group and the nursing staff group revealed that schizophrenic inpatients showed a lower QOL in the domains of physical health and social relationships. Schizophrenia itself and/or accompanying disabilities might induce lower subjective QOL. It is difficult to determine what the important factors are, except for depression, for subjective QOL of schizophrenic inpatients. However, depression should receive more attention for the QOL in the physical health and psychological health domains.

7. 脊髄小脳変性症の失調症状と髄液生化学的パラメーターへの経頭蓋反復磁気刺激の影響

井原雄悦、信国圭吾、高田　裕、坂井研一、西中哲也、田邊康之、高橋幸治

医療 60(4), 233-238, 2006.04

脊髄小脳変性症患者 10 名において失調の重症度,小脳半球血流量,および髄液の ascorbate free radical, superoxide dismutase 蛋白, superoxide 消去能, 8-hydroxy-2'-deoxyguanosine, noradrenaline, dopamine, homovanillic acid, 5-hydroxyindol acetic acid を 8 週間の経頭蓋反復磁気刺激(rTMS)の施行前後で比較した. 脊髄小脳変性症患者では 19 人の対照者に比べて ascorbate free radical, 8-hydroxy-2'-deoxyguanosine, superoxide 消去能が高値を示した. rTMS 後の脊髄小脳変性症患者では ascorbate free radical と失調の重症度が低下し, noradrenaline と dopamine が増加した. しかし rTMS 後に失調の重症度が悪化した唯一の脊髄小脳変性症患者では, ascorbate free radical が増加し, noradrenaline と dopamine が減少していた. したがって, rTMS の治療機序には酸化的ストレスの軽減とカテコラミンの増加が関与していると考えられる.

8. **在宅感染症対策 NPPV を使用している神経疾患患者における呼吸器感染症対策**

   信國圭吾

   難病と在宅ケア 12(10), 43-46, 2007.01

9. **病棟の災害時の防火・避難対策に関する実証的研究 その 1:神経内科病棟における防火・避難対策の実態調査**

   長谷見雄二, 信國圭吾

   早稲田大学理工学術院創造理工学部建築学科研究報告書, 2007.05

10. **岡山県におけるスモン患者の現状**

    井原雄悦

    スモンの過去現在未来(Ⅴ), 2006

11. **中国四国地区におけるスモン患者の現状**

    井原雄悦

    スモンの過去現在未来(Ⅴ), 2006

＜免疫疾患＞

12. **Critical role of the Fc receptor gamma-chain on APCs in the development of allergen-induced airway hyperresponsiveness and inflammation**

    Kitamura K, Takeda K, Koya T, Miyahara N, Kodama T, Dakhama A, Takai T, Hirano A, Tanimoto M, Harada M, Gelfand EW

    J Immunol 178(1), 480-488, 2007

    The FcR common gamma-chain (FcRgamma) is an essential component of the receptors FcepsilonRI, FcgammaRI, and FcgammaRIII, which are expressed on many inflammatory cell types. The role of these receptors in the initiation or maintenance of allergic inflammation has not been well defined. FcRgamma-deficient (FcRgamma(-/-)) and control (wild-type (WT)) mice were sensitized and subsequently

challenged with OVA. Following sensitization and challenge to OVA, FcRgamma-deficient (FcRgamma(-/-)) mice developed comparable levels of IgE and IgG1 as WT mice. However, numbers of eosinophils, levels of IL-5, IL-13, and eotaxin in bronchoalveolar lavage fluid, and mononuclear cell (MNC) proliferative responses to OVA were significantly reduced, as was airway hyperresponsiveness (AHR) to inhaled methacholine. Reconstitution of FcRgamma(-/-) mice with whole spleen MNC from WT mice before sensitization restored development of AHR and the numbers of eosinophils in bronchoalveolar lavage fluid; reconstitution after sensitization but before OVA challenge only partially restored these responses. These responses were also restored when FcRgamma(-/-) mice received T cell-depleted MNC, T and B cell-depleted MNC, or bone marrow-derived dendritic cells before sensitization from FcR(+/+) or FcgammaRIII-deficient but not FcRgamma(-/-) mice. The expression levels of FcgammaRIV on bone marrow-derived dendritic cells from FcR(+/+) mice were found to be low. These results demonstrate that expression of FcRgamma, most likely FcgammaRI, on APCs is important during the sensitization phase for the development of allergic airway inflammation and AHR.

13. Pirfenidone modulates airway responsiveness, inflammation, and remodeling after repeated challenge

Hirano A, Kanehiro A, Ono K, Ito W, Yoshida A, Okada C, Nakashima H, Tanimoto Y, Kataoka M, Gelfand EW, Tanimoto M

Am J Respir Cell Mol Biol 35(3), 366-377, 2006

We investigated the therapeutic potential of a newly developed antifibrotic agent, pirfenidone, to regulate airway remodeling and the development of allergic airway inflammation and airway hyperresponsiveness after chronic allergen challenge. Administration of pirfenidone after sensitization but during the period of ovalbumin challenge significantly prevented the development of airway hyperresponsiveness and prevented eosinophil and lymphocyte accumulation in the airways. IL-4, IL-5, and IL-13 levels in bronchoalveolar lavage fluid and ovalbumin-specific serum IgE antibody levels were also significantly reduced. Treatment with pirfenidone significantly reduced transforming growth factor-beta1 and platelet-derived growth factor levels in bronchoalveolar lavage fluid. Pirfenidone reduced the expression of transforming growth factor-beta1, the development of goblet cell hyperplasia and subepithelial collagenization, and the increases in contractile elements in the lung. These data indicate that pirfenidone may play an important role in the treatment of asthma and has the potential reduce or prevent airway remodeling.

14. The combination effect of amrubicin with cisplatin or irinotecan for small-cell lung cancer cells.

Takigawa N, Takeyama M, Shibayama T, Tada A, Kawata N, Okada C, Aoe K, Kozuki T, Hotta K, Tabata M, Kiura K, Ueoka H, Tanimoto M, Takahashi K

Oncol Rep 15(4), 837-842, 2006

The single agent of amrubicin is active in untreated small-cell lung cancer (SCLC). Cytotoxicity of amrubicinol, the active form of amrubicin, was evaluated in a parent SCLC cell line (SBC-3); an active metabolite of irinotecan, 7-ethyl-10-hydroxy-camptothecin (SN-38)-resistant subline (SBC-3/SN-38);

and cisplatin-resistant subline (SBC-3/CDDP) using AlamarBlue assay. Interaction of the combined drugs was evaluated by median-effect plot analysis, and the fraction of apoptotic cells was determined using flow cytometry. SBC-3/SN-38 was 34-fold more resistant to SN-38 and SBC-3/CDDP was 7.2-fold more resistant to cisplatin than parental SBC-3. However, these resistant sublines retained sensitivity to amrubicinol (1.8- and 1.7-fold, respectively). Simultaneous exposure of SBC-3/SN-38 cells to amrubicinol and cisplatin showed a synergistic effect. Simultaneous exposure of SBC-3/CDDP cells to amrubicinol and SN-38 displayed synergistic or additive effects. The two-drug combination produced an increase of apoptotic cells compared to each single agent alone in both resistant cells. These findings suggest that amrubicin alone and in combination with cisplatin or irinotecan is effective against SCLC refractory to irinotecan and/or cisplatin.

15. 成人喘息―European Community Respiratory Health Survey 調査用紙日本語版の作成と検討

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アレルギー 55(11), 1421-1428, 2006

【目的】成人喘息有病率の国際比較を可能とするために,GINA(Global Initiative for Asthma)で採用されている ECRHS(European Community Respiratory Health Survey)の調査用紙について日本での使用妥当性検証を行った.高齢者での COPD(chronic obstructive pulmonary disease)による喘息類似の症状出現を考慮し,ECRHS オリジナル調査用紙に 2 つの質問事項を追加した.【方法】本研究参加アレルギー呼吸器専門施設において主治医に喘息と診断された患者 370 例,COPD と診断された患者 61 例,非喘息非 COPD(健常群)134 例に対して今回作成した ECRHS 調査用紙日本語版を用いてアンケート調査を依頼しその結果を比較検討した.【結果】過去 12 ヵ月の喘鳴は質問項目中で喘息患者と非喘息健常人との鑑別に最も高い妥当性(感度+特異度)を認め,喘息期間有病率の国際比較の指標として有用であることが示された.一方,特異度は過去 12 ヵ月の胸のつまりによる寝覚めと息切れ発作による寝覚めで高値であった.高齢者では主治医の診断と本人のアンケート上の回答の不一致が若年者と比較して多かったが,この理由としては,患者自身の疾患についての認識の低さや,本調査が,対面式の回答を確認しながらの調査ではない,自記式アンケート調査によったためと考えられた.【結語】本アンケート用紙は,高齢者における精度及び COPD との鑑別の面で問題点は残るも,国際的比較を可能にする点では我が国でも充分使用しうる調査用紙と考えられる.

16. 昆虫アレルギー

宗田 良

今日の治療指針 2007 年版, pp.573-574, 2007.01, 山口徹・北原光夫・福井次矢編, 医学書院, 東京

17. 成人気管支喘息における感作アレルゲンの全国調査

足立 満, 井上洋西, 田村 弦, 佐野靖之, 大田 健, 中川武正, 伊藤幸治, 馬場研二, 平田一人, 東田有智, 中島重徳, 高橋 清, 浅井貞宏, 宮本昭正

アレルギー・免疫 13(4), 548-554, 2006.03

18. 成人喘息の発症・病態における LT 拮抗薬の役割－One airway, One disease－

高橋　清

新居浜市医師会報 590, 11415-11419, 2006

19. 重症難治性喘息治療の再検討　－成人－

高橋　清

THE 26th ROKKO CONFERENCE　気管支喘息のよりよい治療のためにーPharmaco Kinetics, Pharmaco Dynamics からみた喘息治療の再考ー, pp.157-165, 2007.02, 中島重徳・小林節雄・宮本昭正編, ライフサイエンス出版(株), 東京

20. 病態, 発症機序・定義および治療薬剤の奏功機序等について

高橋　清

アレルギー疾患ガイドー発症から予防・治療まで, pp.62-74, 2006, アレルギー疾患ガイド編集委員会編, 中央法規出版(株), 東京

21. プライマリケアにおける高齢者の咳, 痰, 喘鳴の診かた

足立　満, 玉置　淳, 高橋　清, 新実彰男

日経メディカル 11 月号, 219-222, 2006

22. シックハウス症候群と未分類の多種化学物質過敏症の分離の試みーシックハウス症候群の定義および症状ー

鳥居新平, 平山耕一郎, 秋山一男, 池澤善郎, 内尾英一, 岡本美孝, 小倉英郎, 高橋　清, 西間三馨

アレルギー 55(12), 1515-1530, 2006

【目的】シックハウス症候群(SHS)の定義を明らかにする目的で本研究を行った.【方法】SHS の定義は, 1. 発症のきっかけが住居に関連する. 2.症状は住居内で現れる. 3.住居から離れると, 症状は軽くなるか又は消失する. 4.住居に入ると繰り返し症状が現れる. 以上を SHS とし, それ以外は MCS と分類した. SHS のみを完全に抽出すれば, MCS は複数の疾患を含むため, MCS の特徴的な症状は検出され難い. この作業仮説に基づき, オッズ比が, 1 超えが SHS の特徴的な症状となるように, MCS を参照として logistic regression を行った.【結果】オッズ比が 2 以上の SHS に特徴的な症状は吐き気・嘔吐, 何事もおっくうであり, 症状が悪化する原因物質として香水, 化粧品のにおいであった. 各種アレルギー性疾患との比較で, アレルギー疾患に特徴的な症状が夫々検出された.【結語】この結果は, 分類方法が適切であることを示し, 本定義は, WHO のシックビルディング症候群に関する定義と基本的に変わらず, 類似の症状が検出できた.

23. アレルギーの疫学

木村五郎, 高橋　清

からだの科学 252, 6-10, 2007

24. アレルギー科診療のあり方

高橋　清

アレルギー科 21(1), 81-87, 2006

25. 気管支喘息の患者教育　Patient education for bronchial asthma

宗田　良

International Review of Asthma 8, 46-51, 2006

26. 気管支喘息の発作の有無を的確にチェックするには

平野　淳, 高橋　清

モダンフィジシャン 26, 615, 2006

27. 喫煙と喘息

平野　淳, 高橋　清

臨牀と研究 83, 1679-1682, 2006

28. 成人喘息診療の pitfalls

高橋　清

アレルギーの臨床 26(7), 501, 2006

29. 薬剤性喘息患者における喘息治療　ー特にアスピリン喘息についてー

平野　淳, 高橋　清

モダンフィジシャン 26, 850, 2006

＜呼吸器疾患＞

30. Second primary cancer in survivor following concurrent chemoradiation for locally advanced non-small-cell lung cancer

Takigawa N, Kiura K, Segawa Y, Watanabe Y, Kamei H, Moritaka T, Shibayama T, Ueoka H, Gemba K, Yonei T, Tabata M, Shinkai T, Hiraki S, Takemoto M, Kanazawa S, Matsuo K, Tanimoto M, Okayama Lung Cancer Study Group

Br J Cancer 95(9), 1142-1144, 2006. Epub 2006 Oct 10.

Long-term cancer survivors risk development of second primary cancers (SPC). Vigilant follow-up may be required. We report outcomes of 92 patients who underwent chemoradiation for unresectable stage III non-small-cell lung cancer, with a median follow-up of 8.9 years. The incidence of SPC was 2.4 per 100 patient-years (95% confidence interval: 1.0-4.9).

31. A phase I and pharmacological study of amrubicin and topotecan in patients of small-cell lung cancer with relapsed or extensive-disease small-cell lung cancer

Shibayama T, Hotta K, Takigawa N, Tada A, Ueoka H, Harita S, Kiura K, Tabata M, Segawa Y, Nogami N, Kuyama S, Shinkai T, Tanimoto M

Lung Cancer 53(2), 189-195, 2006. Epub 2006 Jun 27.

Cisplatin-based chemotherapy is considered to be a standard treatment in patients with relapsed or extensive-disease (ED) small-cell lung cancer (SCLC), the survival benefit remains modest. Relapsed or ED-SCLC patients were enrolled. Topotecan and amrubicin were administered on Days 1-5 and on Days 3-5, respectively. Nine patients received a total of 24 cycles. Since all three patients experienced dose-limiting toxicity (grade 4 neutropenia lasting for more than 4 days, grade 3 febrile neutropenia, and grade 4 thrombocytopenia) at the third dose level (topotecan: 0.75 mg/m2, amrubicin 40 mg/m2), the maximum tolerated dose was determined to be this dose level. Objective response was observed in six patients (67%). The maximum concentration (Cmax) and area under the plasma concentration-time curve (AUC) of amrubicin increased in a dose-dependent manner. Amrubicin did not influence the pharmacokinetics of topotecan. The Cmax and AUC of amrubicin were correlated with the duration of grade 4 neutropenia. The mean Cmax of topotecan on day 2 in responders (22.9+/-3.6) was significantly higher than that in non-responders (10.9+/-0.4). This phase I study showed the safety and activity of two-drug combination of amrubicin and topotecan in patients with relapsed or ED-SCLC.

32. A triplet chemotherapy with cisplatin, docetaxel and gemcitabine in patients with advanced non-small-cell lung cancer: a phase I/II study

Tabata M, Kozuki T, Ueoka H, Kiura K, Harita S, Tada A, Shibayama T, Takigawa N, Yonei T, Gemba K, Segawa Y, Kishino D, Tada S, Hiraki S, Tanimoto M

Cancer Chemother Pharmacol 60(1), 53-59, 2007. Epub 2006 Sep 29.

We conducted a phase I/II study of triplet chemotherapy consisting of cisplatin (CDDP), docetaxel (DCT) and gemcitabine (GEM) in patients with advanced non-small-cell lung cancer (NSCLC). METHODS: Fifty-three untreated patients with stage IIIB or IV NSCLC were enrolled. All drugs were given on days 1 and 8. The doses of CDDP and DCT were fixed at 40 mg/m(2) and 30 mg/m(2), respectively. In the phase I portion, a dose escalation study of GEM with starting dose of 400 mg/m(2) was conducted and primary objective in the phase II portion was response rate. RESULTS: The maximally tolerated dose (MTD) and recommended dose (RD) of GEM were determined as 800 mg/m(2) because grade 3 non-hematological toxicity (liver damage, diarrhea, and fatigue) developed in three of nine patients evaluated at that dose level. In pharmacokinetic analysis, C (max) and AUC of dFdC and dFdU were increased along with the dose escalation of GEM. However, no relationship between pharmacokinetic parameters and toxicity or response was observed. Objective response rate was 34% and median survival time was 11.7 months. Though major toxicity was myelosuppression, there were no life-threatening toxicities. CONCLUSION: These results indicate that this triplet chemotherapy is feasible and effective in patients with advanced NSCLC.

33. Comprehensive pulmonary rehabilitation according to severity of COPD

Takigawa N, Tada A, Soda R, Takahashi S, Kawata N, Shibayama T, Matsumoto H, Hamada N, Hirano A, Kimura G, Okada C, Endo S, Yamashita M, Date H, Takahashi K

Respir Med 101(2), 326-332, 2007. Epub 2006 Jul 7.

A new classification for the severity of COPD was proposed at GOLD 2003: stage I: FEV(1) > or = 80%

predicted; stage II: 50% < or = FEV(1)<80%; stage III: 30% < or = FEV(1)<50%; and stage IV: FEV(1) < 30%. To elucidate the acute effects of pulmonary rehabilitation (PR) on patients with different stages of COPD, data on pulmonary function, arterial blood gas analysis, the 6-min walk test, respiratory muscle strength, and activities of daily living were analyzed before and after our comprehensive 4- to 8-week inpatient PR program between 1992 and 2003. A total of 225 patients (201 men and 24 women; 21 with stage II, 79 with stage III, and 125 with stage IV COPD) was assessed. There were significant differences in FEV(1)% predicted and % residual volume in stages III and IV, in % vital capacity in stages II, III and IV, and in % total lung capacity in stage II when comparing the changes between pre- and post-PR. Significant differences of PaO(2) in stages III and IV and PaCO(2) in stage IV were found when comparing the changes between pre- and post-PR. The 6-min walk distance was significantly increased after PR by an average of approximately 50m for all staged patients. Respiratory muscle strength was also significantly increased in stages III and IV. Activities of daily living were significantly improved in all stages. These results showed that patients with COPD had benefited from PR regardless of disease severity. The effects included improvement in pulmonary function, arterial blood gas analysis, 6-min walk distance, respiratory muscle strength, and activities of daily living although there were some differences among the three stages.

34. Distance and oxygen desaturation in 6-min walk test predict prognosis in COPD patients

Takigawa N, Tada A, Soda R, Date H, Yamashita M, Endo S, Takahashi S, Kawata N, Shibayama T, Hamada N, Sakaguchi M, Hirano A, Kimura G, Okada C, Takahashi K

Respir Med 101(3), 561-567, 2007. Epub 2006 Aug 8.

The aim of the present study was to predict the prognosis of Chronic obstructive pulmonary disease (COPD) patients who underwent comprehensive pulmonary rehabilitation (PR). A total of 144 patients who performed PR between 1992 and 1999 was assessed. After PR, 67 patients underwent lung volume reduction surgery (LVRS). Baseline data before PR consisted of body mass index, serum albumin levels, use of supplement oxygen at home, pulmonary function, arterial blood gas analysis, and distance and fall of hemoglobin oxygen saturation (DeltaSpO(2)) in 6-min walk test. In addition to pre-PR factors, treatment with LVRS was taken into the analysis. The prognostic significance of variables influencing survival was determined by univariate analysis with Log rank test or multivariate analysis using Cox's proportional hazard model. By a median follow-up time of 8.4 years, the median survival time was 8.1 years (95% confidence interval: 6.9-9.4 years). Albumin level, PaCO(2), distance and DeltaSpO(2) were significant prognostic factors in univariate analysis. LVRS did not affect the prognosis. The multivariate analysis showed short distance and increase of DeltaSpO(2) as significant independent predictors of the risk of death. 6-min walk test was very useful for predicting the prognosis of the COPD patients.

35. Influence of altering administration sequence of docetaxel, gemcitabine and cisplatin in patients with advanced non-small cell lung cancer

Harita S, Kiura K, Tabata M, Takigawa N, Kuyama S, Kozuki T, Kamei H, Tada A, Okimoto N, Gemba K, Tada S, Ueoka H, Hiraki S, Tanimoto M

Anticancer Res 26(2B), 1637-1641, 2006

A phase II study of a triplet chemotherapy with the administration sequence of gemcitabine (GEM), docetaxel (DCT) and cisplatin (CDDP) (OLCSG9908) was previously conducted in patients with advanced non-small cell lung cancer (NSCLC). The objective response rate was 34% and the median survival time (MST) and 1-year survival rate were 11.7 months and 49%, respectively. In an in vitro study of different sequence exposures to GEM and DCT, it was reported that the synergistic effect was more prominent using the administration sequence of DCT followed by GEM compared with the reverse sequence. In order to estimate the effects of the administration sequence, a phase II study of the same triplet chemotherapy was conducted with the administration sequence of DCT, CDDP and GEM. PATIENTS AND METHODS: Patients with unresectable stage IIIB/IV NSCLC were eligible. All drugs were given intravenously on days 1 and 8, and repeated every 4 weeks for up to 4 cycles. DCT (30 mg/m2) was given first, followed by CDDP (40 mg/m2) and GEM (800 mg/m2). RESULTS: Thirty-four patients were enrolled on this study (OLCSG0101). The objective response rate was 38% (95% CI: 22-56%). As grade 3/4 hematological toxicities, neutropenia, thrombocytopenia and anemia were observed in 70%, 41% and 21%, respectively, and febrile neutropenia was observed in 12%. As grade 3/4 non-hematological toxicities, vomiting and liver dysfunction were observed in 15% and 18%, respectively. These toxicities were manageable by conventional therapy. The MST and 1-year survival rate were 13.3 months (95% CI: 7.8-18.7 months) and 55% (95% CI: 38-73%), respectively. These results were similar to those of OLCSG9908. CONCLUSION: This triplet chemotherapy is well tolerated and effective in patients with advanced NSCLC, however, the treatment outcome was not significantly influenced by the administration sequence of DCT and GEM.

36. **Triple combination chemotherapy with cisplatin, docetaxel, and irinotecan for advanced non-small cell lung cancer: a phase I/II trial.**

Kiura K, Takigawa N, Segawa Y, Tabata M, Shibayama T, Gemba K, Bessho A, Fujimoto N, Takata I, Hotta K, Fujiwara K, Tokuda Y, Kuyama S, Shinkai T, Ueoka H, Tanimoto M; Okayama Lung Cancer Study Group.

J Thorac Oncol 2(1), 44-50, 2007

BACKGROUND: To determine the recommended dose and evaluate the response rate and toxicity of triplet chemotherapy using cisplatin, docetaxel, and irinotecan for non-small cell lung cancer (NSCLC) patients with stage IIIB or IV. METHODS: A total of 65 patients (33 men and 32 women) with advanced NSCLC, a good performance status, and 65 years of age or younger were included in these phase I/II studies. The median age was 52 years. Most patients had performance status 1 (49/65) and stage IV disease (49/65). Adenocarcinoma was the most common tumor histology (55 patients). Cisplatin and docetaxel were given on day 1 and irinotecan on day 2; the cycles were repeated every 3 weeks. RESULTS: In the phase I study, the maximum tolerated doses of combination cisplatin/docetaxel/irinotecan were, respectively, 80/60/60 (mg/m) and the recommended doses for the phase II study were determined to be 60/60/60 (mg/m), respectively. The dose-limiting toxicities were neutropenia, neutropenic fever, and diarrhea. In the phase II study, 157 cycles of chemotherapy were delivered to 49 patients (median three cycles per patient). The objective response rate was 57.1% (95% confidence interval: 43.1%-71.1%). The

median survival time and the actual 2-, 3- and estimated 5-year survival rates were 17 months, 33%, 25%, and 18%, respectively. Grade 3/4 toxicities consisted of neutropenia (92%), neutropenic fever (45%), nausea/vomiting (27%), diarrhea (35%), and hepatic toxicity (2%); there were no cases of treatment-related death. CONCLUSION: This triplet chemotherapy has shown a promising activity against advanced NSCLC according to admission-based treatment with adequate supportive care. The principal toxicity was neutropenic fever, but supportive care should be explored to reduce this incidence.

37. BrothMIC NTM を用いた非結核性抗酸菌の薬剤感受性についての検討

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結核　81(4), 329-335, 2006

BrothMIC NTM を用いた非結核性抗酸菌(NTM)の薬剤感受性について検討した. 方法は, 治療歴の全くない患者の喀痰から分離された M. avium31 株, M.intracellulare44 株, M.kansasii17 株を対象に, 微量液体希釈法による BrothMIC NTM を用いて抗結核薬(streptomycin:SM, ethambutol: EB, kanamycin: KM, isoniazid: INH, rifampicin: RFP), ニューマクロライド薬(clarithromycin: CAM), ニューキノロン薬(levofloxacin: LVFX, gatifloxacin: GFLX)の計 8 剤に対する MIC を測定した. RFP, CAM, LVFX, GFLX の 4 剤は 3 菌種すべてに MIC が低く, 強力な抗菌活性を有しており, ニューキノロン薬では GFLX が LVFX より 3 菌種とも MIC が低く, より優れた抗菌活性を示した. EB, INH の MIC は M.avium, M.intracellulare で高かった.

38. 多剤耐性結核に対する ofloxacin, levofloxacin の in vitro 抗菌活性と臨床効果

多田敦彦, 河田典子, 柴山卓夫, 高橋秀治, 平野　淳, 木村五郎, 竹内　誠, 岡田千春, 宗田　良, 高橋　清

結核　81(4), 337-344, 2006

多剤耐性結核に対する ofloxacin(OFLX), levofloxacin(LVFX)の in vitro 抗菌活性と臨床効果について検討した. 対象は, isoniazid(INH)と rifampicin(RFP)の両剤に完全耐性の多剤耐性結核患者 46 例(男性 33 例, 女性 13 例・平均年齢 60.6 歳)で, OFLX・LVFX の薬剤感受性試験を行なった. OFLX・LVFX 耐性の頻度は持続排菌群 35%(7/20), キノロン系薬前治療あり群 42%(5/12)と高頻度であった. 診断直後に転院した 1 例を除く 45 例の治療効果は, 34 例(76%)で排菌停止を認めた. 内訳は OFLX・LVFX を含む治療 34 例中 28 例, OFLX・LVFX 非使用 11 例中 6 例であった. 再排菌を 9 例(OFLX・LVFX 使用 7 例, OFLX・LVFX 非使用 2 例)に認めた. 治療失敗や再発の危険因子は, 単変量解析では OFLX・LVFX 耐性・広汎な病変・感受性薬剤数 4 剤以下の 3 項目で, 多変量解析では OFLX・LVFX 耐性のみであった. 経過中 18 例(40%)が死亡し, うち 10 例が結核死であった. 50%生存期間は 92.6 ヵ月(排菌停止群 122.8 ヵ月, 治療失敗群 68.5 ヵ月)であった.

＜がん・血液疾患＞

39. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group.

Yanada M, Takeuchi J, Sugiura I, Akiyama H, Usui N, Yagasaki F, Kobayashi T, Ueda Y, Takeuchi M, Miyawaki S, Maruta A, Emi N, Miyazaki Y, Ohtake S, Jinnai I, Matsuo K, Naoe T, Ohno R; Japan Adult Leukemia Study Group.

J Clin Oncol 24(3), 460-6, 2006. Epub 2005 Dec 12.

PURPOSE: A novel therapeutic approach is urgently needed for BCR-ABL-positive acute lymphoblastic leukemia (ALL). In this study, we assessed the efficacy and feasibility of chemotherapy combined with imatinib. PATIENTS AND METHODS: A phase II study of imatinib-combined chemotherapy was conducted for newly diagnosed BCR-ABL-positive ALL in adults. Eighty patients were entered into the trial between September 2002 and January 2005. RESULTS: Remission induction therapy resulted in complete remission (CR) in 77 patients (96.2%), resistant disease in one patient, and early death in two patients, as well as polymerase chain reaction negativity of bone marrow in 71.3%. The profile and incidence of severe toxicity were not different from those associated with our historic chemotherapy-alone regimen. Relapse occurred in 20 patients after median CR duration of 5.2 months. Allogeneic hematopoietic stem-cell transplantation (HSCT) was performed for 49 patients, 39 of whom underwent transplantation during their first CR. The 1-year event-free and overall survival (OS) rates were estimated to be 60.0%, and 76.1%, respectively, which were significantly better than those for our historic controls treated with chemotherapy alone ($P < .0001$ for both). Among the current trial patients, the probability for OS at 1 year was 73.3% for those who underwent allogeneic HSCT, and 84.8% for those who did not. CONCLUSION: Our results demonstrated that imatinib-combined regimen is effective and feasible for newly diagnosed BCR-ABL-positive ALL. Despite a relatively short period of observation, a major potential of this treatment is recognized. Longer follow-up is required to determine its overall effect on survival.

40. The prophylactic effect of Itraconazole capsules and Fluconazole capsules for systemic fungal infections in patients with acute myeloid leukemia and myelodyplastic syndromes: A Japanese multicenter randomized, controlled study

Ito Y, Ohyashiki K, Yoshida I, Takeuchi M, Aoyama Y, Mugitani A, Matsuura Y, Wakita H, Matsuda M, Sakamoto E, Kiguchi T, Urabe A, Tamura K, Kanamaru A, Masaoka T, The Japan Febrile Neutropenia Study Group

Int J Hematol 85(2), 121-127, 2007

We performed a randomized, controlled study comparing the prophylactic effects of capsule forms of fluconazole (n = 110) and itraconazole (n = 108) in patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) during and after chemotherapy. There were 4 cases with possible systemic fungal infection in the itraconazole group, and there were 8 possible and 3 probable cases in the fluconazole group. Adverse events did not significantly differ in the 2 groups. In patients with MDS or in the remission-induction phase of chemotherapy, the numbers of cases with probable or possible infections were lower in the itraconazole group than in the fluconazole group, whereas no difference was seen in patients with AML or in the consolidation phase of therapy. In patients with neutrophil counts of >0.1 x 10(9)/L lasting for more than 4 weeks, the frequency of infection in the fluconazole group (5 of 9 patients) was

significantly higher than in the itraconazole group (0 of 7 patients; P = .03). Our results suggest that both drugs were well tolerated in patients with AML or MDS who received chemotherapy and that the efficacy of itraconazole for prophylaxis against systemic fungal disease is not inferior to that of fluconazole.

41. Recent improvement in lung cancer screening: A comparison of the results carried out in two different time periods

Kitajima T, Nishii K, Ueoka H, Shibayama T, Gemba K, Kodani T, Kiura K, Tabata M, Hotta K, Tanimoto M, Sobue T

Acta Med Okayama 60(3), 173-179, 2006

To evaluate recent improvements in lung cancer screening, we compared the results of recently conducted lung cancer screening with those of a previous screening. This study compared the survival of lung cancer patients detected by lung cancer screening conducted between 1976 and 1984 (early period) with that conducted between 1989 and 1997 (late period). Two hundred seventy-six patients with lung cancer were detected in the early period and 541 patients with lung cancer were detected in the late period. The median survival time (late: 49.8 vs. early: 27.8 months) and the 5-year survival rate (late : 47.8 vs. early : 34.8%) of the patients with lung cancer detected in the late period were significantly better than those in the early period (p = 0.0054). Among patients undergoing resection, the proportion of pathological stage I patients in the late period was significantly higher than that in the early period (late: 60.8 vs. early : 54.9%, p = 0.005). Multivariate analysis showed that the screening time period was a significant prognostic factor (hazard ratio = 0.685, 95% confidence interval: 0.563-0.832, p = 0.0002). These results were consistent with the findings of case-control studies of lung cancer screening programs in the late period recently conducted in Japan, which also showed a greater efficacy for screening than for previous case-control studies in the early period.

42. タミバロテン(Am-80)による再発・難治性 APL(急性前骨髄球性白血病)治療の実際

竹内 誠

血液フロンティア 16(9), 161-168, 2006

＜耳鼻科＞

43. Expression of IL-12 and T helper cell 1 cytokines in the fluid of paranasal sinus mucoceles

Kariya S, Okano M, Hattori H, Sugata Y, Matsumoto R, Fukushima K, Akagi H, Nishizaki K

Am J Otolaryngol 28(2), 83-86, 2007

The objective of this study was to assess the expression of regulatory cytokines and T helper cell(Th)1/Th2 cytokines in paranasal sinus mucoceles. Materials and methods: Fluid samples of 12 paranasal sinus mucoceles were assessed by enzyme-linked immunosorbent assay for concentrations of regulatory cytokines (interleukin [IL]-10 and IL-12), Th1 cytokines (IL-2 and interferon gamma), and Th2 cytokines (IL-4 and IL-5). Results: IL-12 was detected in all samples, whereas IL-10 was detected in only one case. The concentration of IL-12 tended to correlate with that of interferon gamma and was

significantly and positively correlated with that of IL-2. Conclusions: Th1 cytokines and the Th1 regulatory cytokine IL-12, but not IL-10, potentially play a key role in the pathogenesis of paranasal sinus mucoceles. Together with our recent report showing that lipopolysaccharide is highly detected in mucocele fluid, the data from this study suggest that the Th1 response induced by lipopolysaccharide may affect the immunological inflammation in the epithelium of paranasal sinus mucoceles.

44. 耳下腺部腫瘤に対する当科の取り組みと現況 ―手術療法を中心にした検討―

土井　彰, 田村耕三, 沼本　敏, 岩田　純, 小川晃弘, 赤木博文, 西崎和則

高知医療センター医学雑誌 1(1), 3-9, 2006.09

＜看護部＞

45. 全身麻酔下肺切除術患者の側臥位固定時の看護師の行動分析 ビデオからリスク回避を言語化して

竹田明仁, 溝内育子, 黒崎美紀, 田本真理子

国立病院看護研究学会誌 3, 21-26, 2007

1.全身麻酔下肺切除患者の側臥位体位固定時の看護師の行動分析を目的とし，手術室看護師に対しビデオ撮影という方法で研究を行った。2.手術時側臥位固定時に看護師がとっているリスク回避行動として【1 転落】【2 ルート･コード類の抜去】【3 呼吸管理障害】【4 手術部位の誤手術】【5 身体損傷】【6 神経障害】【7 脱臼】【8 体位変換による状態の急変】【10 コミュニケーション不足】【11 所要時間の延長】の 11 項目が抽出できた。

＜小児科＞

46. Clinical Significance of Decreased Serum Concentration of Cartilage Oligomeric Matrix Protein in Systemic Juvenile Idiopathic Arthritis

Urakami T, Manki A, Inoue T, Oda M, Tanaka H, Morishima T

J Rheumatol 33(5), 996-1000, 2006

Serum cartilage oligomeric matrix protein (COMP) concentration is elevated in patients with early osteoarthritis and early rheumatoid arthritis, and may be a biomarker of cartilage turnover. We investigated whether serum COMP concentration could be a clinically significant marker of arthritis and/or growth impairment in juvenile idiopathic arthritis (JIA). METHODS: Specimens were collected from 82 healthy blood donors under 22 years of age with no growth impairment who served as healthy controls, and from 24 patients with JIA (6 with oligoarthritis, 10 with polyarthritis, 8 with systemic JIA) presenting with active arthritis. Serum COMP concentration was determined using a human COMP assay kit. RESULTS: Serum COMP concentrations were significantly higher in all controls less than 16 years of age than in all controls aged 16 years or older. There was a significant negative correlation between serum COMP concentration and serum C-reactive protein in patients with JIA. Serum COMP concentrations in patients with systemic JIA were significantly lower than those in controls. CONCLUSION: Serum COMP concentrations in healthy children reflected increased cartilage turnover in the growth phase. Because the serum COMP concentration was decreased in cases of systemic JIA in which growth impairment was

pronounced, the systemic inflammation occurring in systemic JIA may have an effect on cartilage turnover, which plays an important role in growth. Serum COMP concentration may prove to be a marker that indicates growth impairment in systemic JIA.

＜整形外科＞

47. 症例 10 *M. intracellulare* による脊椎炎

太田裕介

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