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# 進行癌患者に対する、 低分子フコイダン(LMF)による 抗炎症作用に関する探索的検討報告

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LMF (Low-Molecular-Fucoidan) 研究会

# ***Cladosiphon* including fucoidan** (いわゆる“モズク”)



Fucoidan exhibits broad biological activities in basic research; such as anti-cancer, anti-oxidant and anti-inflammatory effects.

## Fucoidan reduces the toxicities of chemotherapy for patients with unresectable advanced or recurrent colorectal cancer

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**Abstract.** Combination chemotherapy with oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) or irinotecan plus 5-fluorouracil/leucovorin (FOLFIRI) has become a standard regimen for advanced or recurrent colorectal cancer. Numerous studies have reported that long-term use of FOLFOX or FOLFIRI leads to better survival for these patients. Thus, control of the toxicity of these drugs may be crucial to prolonging survival. Fucoidan is one of the major sulfated polysaccharides of brown seaweeds and exhibits a wide range of biological activities. In the present study, we analyzed the effect of fucoidan on suppressing the toxicity of anti-cancer drugs. A total of 20 patients with unresectable advanced or recurrent colorectal cancer scheduled to undergo treatment with FOLFOX or FOLFIRI were randomly allocated into a fucoidan treatment group (n=10) and a control group without fucoidan treatment (n=10). Results showed that fucoidan regulated the occurrence

(LV) (FOLFOX) or irinotecan plus 5-FU/LV (FOLFIRI) has become the standard regimen for advanced or recurrent colorectal cancer, and a high response rate has been reported (1-3). However, FOLFOX and FOLFIRI are associated with severe toxicity, such as nausea, vomiting, stomatitis, diarrhea, fatigue, neutropenia, anemia, thrombocytopenia and liver dysfunction. A number of patients discontinue these effective chemotherapies due to toxicity. Thus, the prognosis of patients with unresectable advanced or recurrent colorectal cancer remains low despite advances in chemotherapeutic drugs.

To reduce the toxicity of chemotherapeutic drugs, various types of drugs or dietary supplements have been introduced (4-6). Among these supplements, fucoidan has been reported to exhibit anti-inflammatory, antiviral and anti-tumor activities (7-9). Fucoidan is a sulfated polysaccharide found mainly in various species of brown seaweeds such as kombu, wakame,

# ＜進行大腸癌患者に対するRCT＞ Cx (FOLFOX/FOLFILI) ± フコイダン

- Cxの副作用のうち「倦怠感」が、フコイダン群で有意に少なかった(p=0.019)
- 生存期間で、フコイダン群の方が優れている傾向(p=0.314)

Table II. Major adverse events.<sup>a</sup>

|                       | + Fucoidan | - Fucoidan | P-value      |
|-----------------------|------------|------------|--------------|
| No. of patients       | 10         | 10         |              |
| Leukocytopenia        | 1          | 0          | 0.305        |
| Neutropenia           | 3          | 4          | 0.639        |
| Anemia                | 2          | 1          | 0.531        |
| Thrombocytopenia      | 0          | 2          | 0.136        |
| Nausea                | 1          | 1          | 1.000        |
| Diarrhea              | 1          | 2          | 0.531        |
| Stomatitis            | 3          | 1          | 0.264        |
| <u>Fatigue</u>        | <u>1</u>   | <u>6</u>   | <u>0.019</u> |
| Peripheral neuropathy | 3          | 5          | 0.361        |
| Liver dysfunction     | 0          | 2          | 0.136        |

<sup>a</sup>Adverse events ≥2.

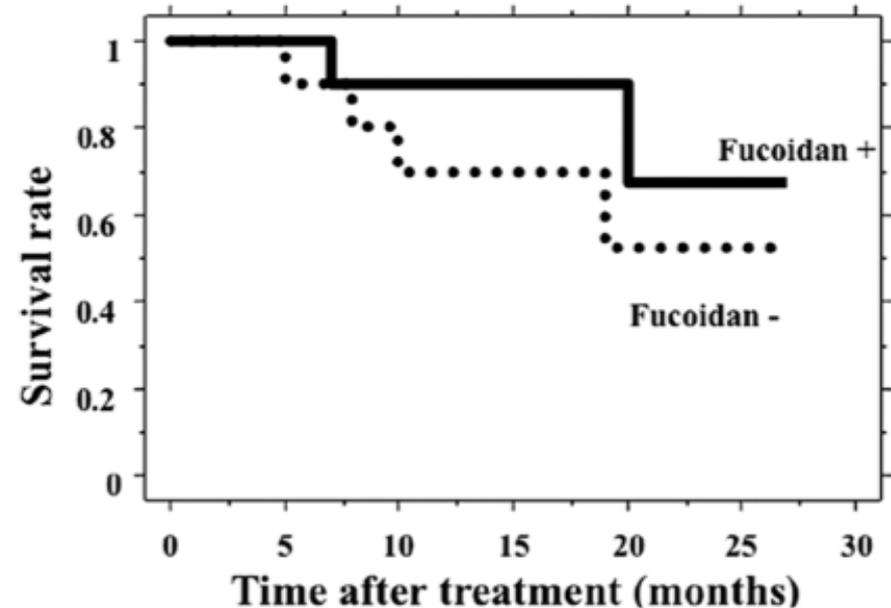


Figure 1. Survival curves of advanced or recurrent colorectal cancer patients. Solid line, survival curve of 10 patients who received fucoidan treatment. Dotted line, survival curve of 10 patients who did not receive fucoidan treatment. The difference was not significant (P=0.314).

Full-Length Review

## The association between fatigue and inflammatory marker levels in cancer patients: A quantitative review

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### Abstract

Increased cytokine and neopterin levels may be responsible for cancer-related fatigue, the most common complaint among cancer patients. We quantitatively reviewed empirical findings on this topic, focusing on studies not using immunotherapy. PubMed, PsychINFO and BIOSIS were searched for articles published until July 2006. Studies remained unweighted or were weighted according to study quality and sample size. The correlation coefficient  $r$  was used for statistical analyses. Heterogeneity among the studies was examined using the  $I^2$  index. Eighteen studies (1037 participants) of moderately high methodological quality were located and statistically analyzed. Most studies measured more than one inflammatory marker, resulting in a total of 58 correlation estimates. In 31 of these, we had to impute a null correlation because results had been simply reported as nonsignificant and no further statistical information was available. General analyses based on weighting according to sample size showed a significantly positive correlation between fatigue and circulating levels of inflammatory markers ( $r = 0.11$ ,  $p < 0.0001$ ). Analyses of individual inflammatory markers revealed significantly positive correlations between fatigue and IL-6 ( $r = 0.12$ ,  $p = 0.004$ ), fatigue and IL-1ra ( $r = 0.24$ ,  $p = 0.0005$ ), and fatigue and neopterin ( $r = 0.22$ ,  $p = 0.0001$ ). Fatigue did not correlate significantly with IL-1 $\beta$  ( $r = 0.05$ ,  $p = 0.42$ ) or TNF- $\alpha$  ( $r = 0.04$ ,  $p = 0.34$ ). Given its preliminary nature due to the limited available data, this quantitative review showed a positive association between cancer-related fatigue and circulating levels of IL-6, IL-1ra and neopterin. Future studies examining the relationship between cancer related fatigue and inflammation would benefit from multiple rather than single blood sampling and from repeated daily ratings of the multidimensional nature of fatigue.

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**Keywords:** Cancer; Cytokines; Fatigue; Interleukin; Quantitative review; Quality of life; Tumor necrosis factor

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# 仮 説

フコイダンは、

進行がん患者において

抗炎症作用を発揮しうるか

# 方 法

- 多施設共同・前向き臨床研究として、倫理委員会の承認を経て行われた。
- 患者登録期間は2014年1月～2015年2月の1年間。
- 本試験参加を希望するがん患者に、同意のもとフコイダンサプリメント（パワーフコイダン®）を400ml/日、少なくとも1ヶ月間、服用してもらった。
- 服用開始前、2週間後、4週間後に外来診察時に以下について評価。

## <主要評価項目>

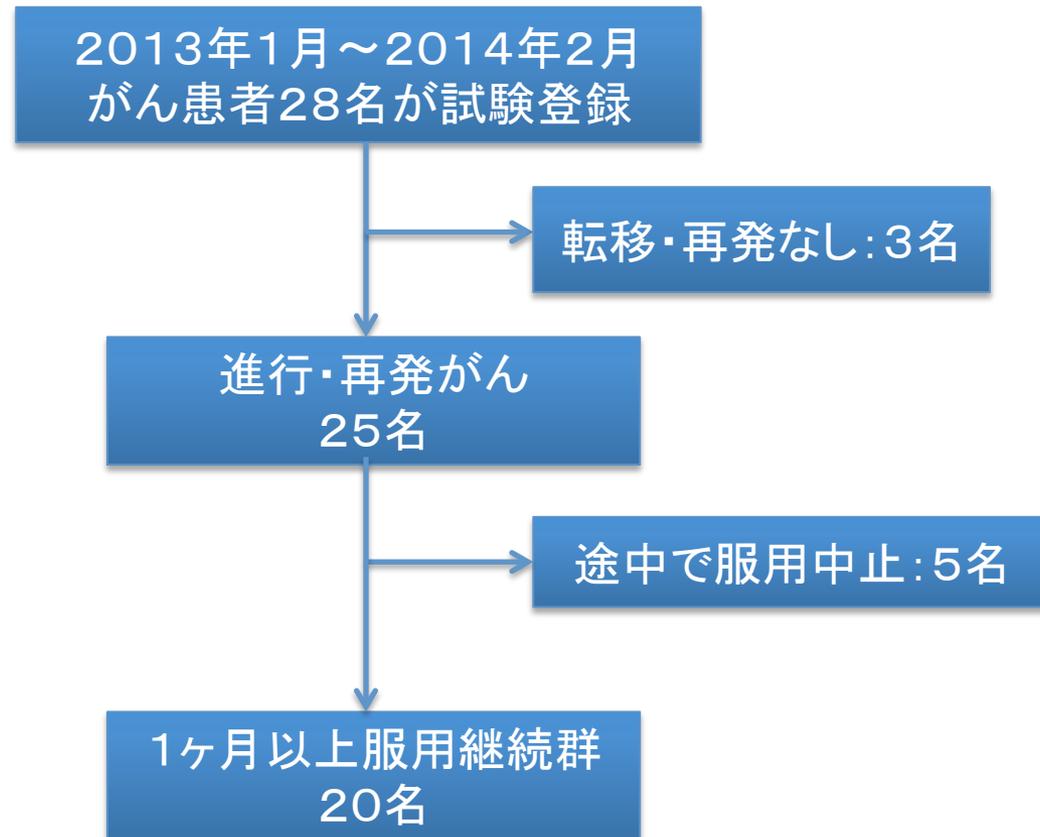
WBC数, N/L比, CRP, リンパ球分画, サイトカイン(IL-1 $\beta$ 、IL-6、TNF- $\alpha$ )

※解析は(株)健康ライフサイエンス社に依頼

## <副次評価項目>

「EORTC QLQ-C30」を用いたQOL評価

# Flow Diagram of the patients



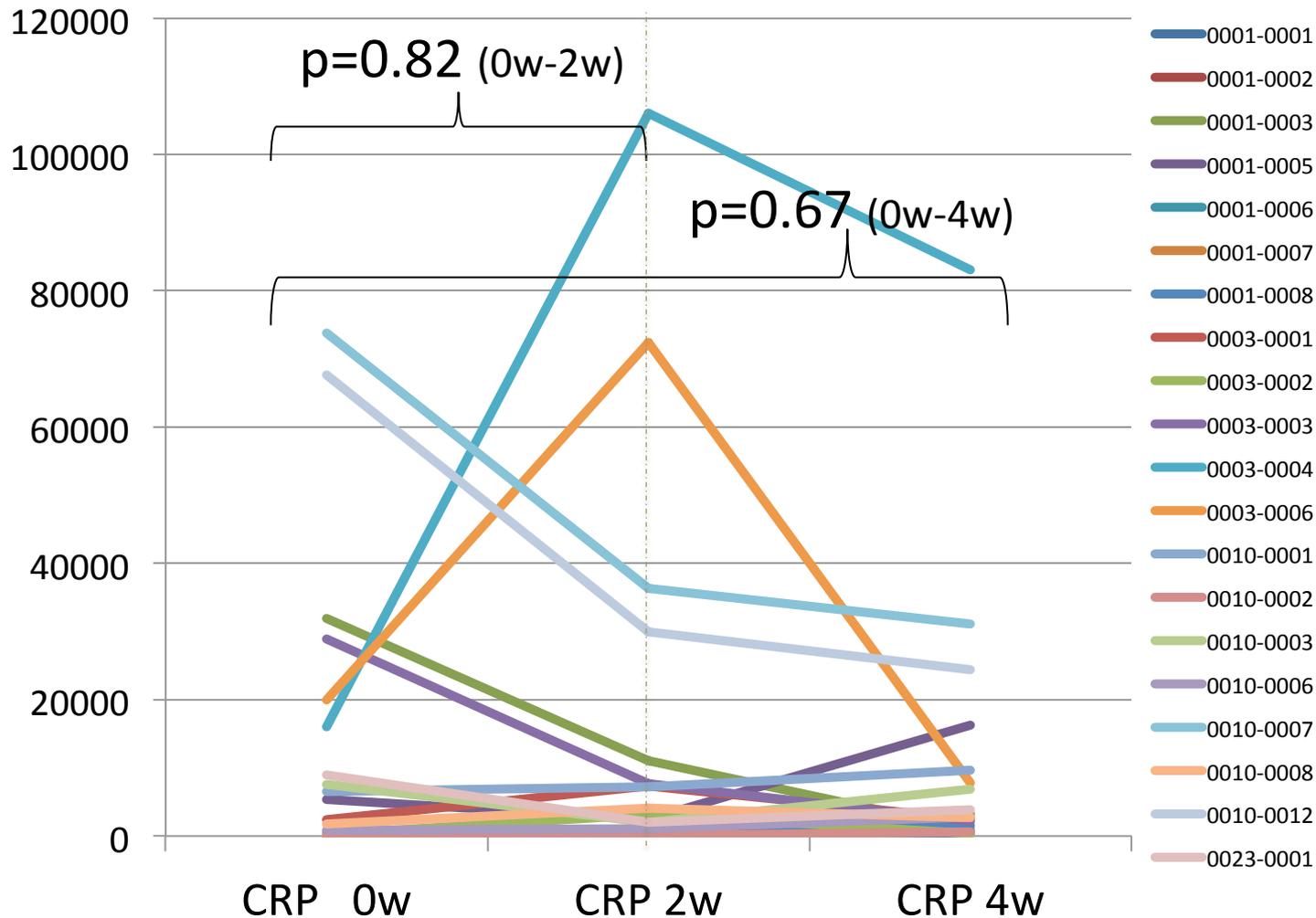
# 患者背景

| N=20                                |                         | N (=20)              | % (=100%) |
|-------------------------------------|-------------------------|----------------------|-----------|
| Age (range)                         |                         | 58.9 (18-76)         |           |
| Sex                                 | male                    | 12                   | 60.0%     |
|                                     | female                  | 8                    | 40.0%     |
| Primary Diagnosis                   | lung                    | 4                    | 20.0%     |
|                                     | colon                   | 4                    | 20.0%     |
|                                     | liver                   | 2                    | 10.0%     |
|                                     | stomach                 | 2                    | 10.0%     |
|                                     | pancreas                | 2                    | 10.0%     |
|                                     | sarcoma                 | 2                    | 10.0%     |
|                                     | uterus                  | 1                    | 5.0%      |
|                                     | breast                  | 1                    | 5.0%      |
|                                     | prostate                | 1                    | 5.0%      |
|                                     | Head&neck               | 1                    | 5.0%      |
| Histology                           | adenocarcinoma          | 13                   | 65.0%     |
|                                     | squamous cell carcinoma | 3                    | 15.0%     |
|                                     | others                  | 4                    | 20.0%     |
| Anticancer therapy before the trial | surgery                 | 10                   | 50.0%     |
|                                     | chemotherapy            | 18                   | 90.0%     |
|                                     | radiotherapy            | 4                    | 20.0%     |
| Baseline laboratory data            | WBC                     | 6135 ( $\pm$ 3519)   |           |
|                                     | Hb                      | 11.2 ( $\pm$ 1.9)    |           |
|                                     | Plt                     | 23.1 ( $\pm$ 13.3)   |           |
|                                     | Neu%                    | 58.2 ( $\pm$ 14.2)   |           |
|                                     | Lym%                    | 29.5 ( $\pm$ 14.1)   |           |
|                                     | 高感度CRP                  | 20019 ( $\pm$ 33133) |           |
|                                     | Alb                     | 3.9 ( $\pm$ 0.5)     |           |

# 結果①：血算、N/L比、CRP、リンパ球分画の変化

| N=20                     |                          | 0w                | 2w                | 4w                | p値(0w-2w) | p値(0w-4w) |
|--------------------------|--------------------------|-------------------|-------------------|-------------------|-----------|-----------|
| Baseline laboratory data |                          |                   |                   |                   |           |           |
|                          | WBC                      | 6135 (±3519)      | -                 | 6195 (±3148)      | -         | 0.9365    |
|                          | Hb                       | 11.2 (±1.9)       | -                 | 11.4 (±1.9)       | -         | 0.6442    |
|                          | Plt                      | 23.1 (±13.3)      | -                 | 24.9 (±17.2)      | -         | 0.4996    |
|                          | Neu%                     | 58.2 (±14.2)      | -                 | 56.1 (±14.4)      | -         | 0.6384    |
|                          | Lym%                     | 29.5 (±14.1)      | -                 | 31.0 (±10.9)      | -         | 0.7178    |
|                          | N/L                      | 2.7 (±1.8)        | -                 | 2.3 (±1.6)        | -         | 0.4221    |
|                          | 高感度CRP                   | 20019<br>(±33133) | 21494<br>(±38580) | 17738<br>(±37284) | 0.8152    | 0.6738    |
| リンパ球分画                   |                          |                   |                   |                   |           |           |
|                          | T cell (CD3+) (%)        | 68.8 (±13.0)      | -                 | 64.7 (±14.2)      | -         | 0.0606    |
|                          | B cell (CD20+) (%)       | 11.3 (±9.6)       | -                 | 10.9 (±11.5)      | -         | 0.8095    |
|                          | NK cell (%)              | 21.2 (±13.4)      | -                 | 25.1 (±13.2)      | -         | 0.1096    |
|                          | CD4+ T (%)               | 41.4 (±10.7)      | -                 | 37.6 (±11.0)      | -         | 0.0929    |
|                          | CD8+ T (%)               | 23.2 (±4.4)       | -                 | 24.5 (±7.6)       | -         | 0.3314    |
|                          | CD4 Naïve T (%)          | 32.5 (±13.6)      | -                 | 31.5 (±14.3)      | -         | 0.3547    |
|                          | CD4 Memory T (%)         | 67.5 (±13.6)      | -                 | 68.5 (±14.3)      | -         | 0.3547    |
|                          | Treg (CD4+CD25+) (%)     | 5.6 (±3.3)        | -                 | 7.1 (±4.7)        | -         | 0.1706    |
|                          | CD8+CD28+ T (%)          | 58.5 (±19.7)      | -                 | 51.5 (±17.1)      | -         | 0.0463    |
|                          | NK(CD56+CD16+)           |                   |                   |                   |           |           |
|                          | Perforin+ GranzymeB+ (%) | 89.8 (±15.3)      | -                 | 89.8 (±11.7)      | -         | 0.991     |

# <高感度CRP推移(例:1000ng/ml=0.1mg/dl):全20名>



開始後2週間での「CRP」改善率: 50% (10/20人)  
※統計学的有意差はなし。

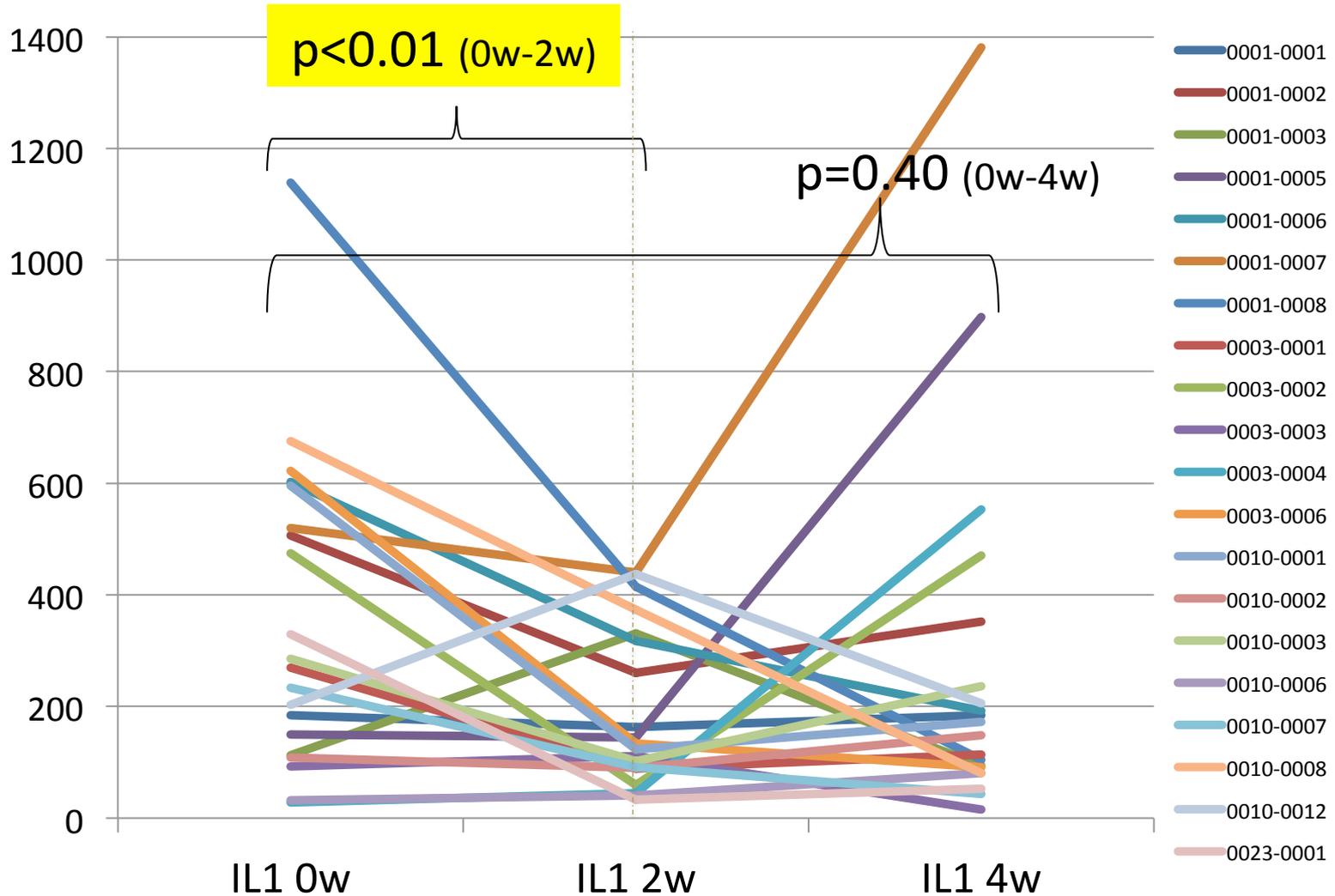
## 結果②: サイトカインの変化

| N=20   |                          | 0w                        | 2w                        | 4w                        | p値(0w-2w) | p値(0w-4w) |
|--------|--------------------------|---------------------------|---------------------------|---------------------------|-----------|-----------|
| サイトカイン | IL-1 $\beta$<br>(pg/ml)  | 358.2<br>( $\pm$ 280.4)   | 189.9<br>( $\pm$ 143.0)   | 273.4<br>( $\pm$ 336.4)   | 0.0057*   | 0.3987    |
|        | IL-6<br>(pg/ml)          | 2198.6<br>( $\pm$ 2523.6) | 1522.8<br>( $\pm$ 1641.4) | 1624.1<br>( $\pm$ 1347.6) | 0.0311*   | 0.2429    |
|        | TNF-alpha<br>(pg/ml)     | 4819.4<br>( $\pm$ 3452.6) | 3257.2<br>( $\pm$ 2900.5) | 3985.1<br>( $\pm$ 2453.4) | 0.0338*   | 0.1524    |
|        | IFN-gamma<br>(pg/ml)     | 2060.4<br>( $\pm$ 1274.7) | 1762.8<br>( $\pm$ 1186.4) | 2048.3<br>( $\pm$ 1212.8) | 0.1799    | 0.9651    |
|        | IL-2<br>(pg/ml)          | 396.5<br>( $\pm$ 553.6)   | 292.3<br>( $\pm$ 397.4)   | 421.4<br>( $\pm$ 610.2)   | 0.0632**  | 0.8099    |
|        | IL-17<br>(pg/ml)         | 81.0<br>( $\pm$ 74.8)     | 92.7<br>( $\pm$ 95.1)     | 101<br>( $\pm$ 88.8)      | 0.4949    | 0.3768    |
|        | IL12/IL-23p40<br>(pg/ml) | 138.4<br>( $\pm$ 87.4)    | 97.8<br>( $\pm$ 70.2)     | 100.9<br>( $\pm$ 80.3)    | 0.0587**  | 0.0565    |

\*p<0.05

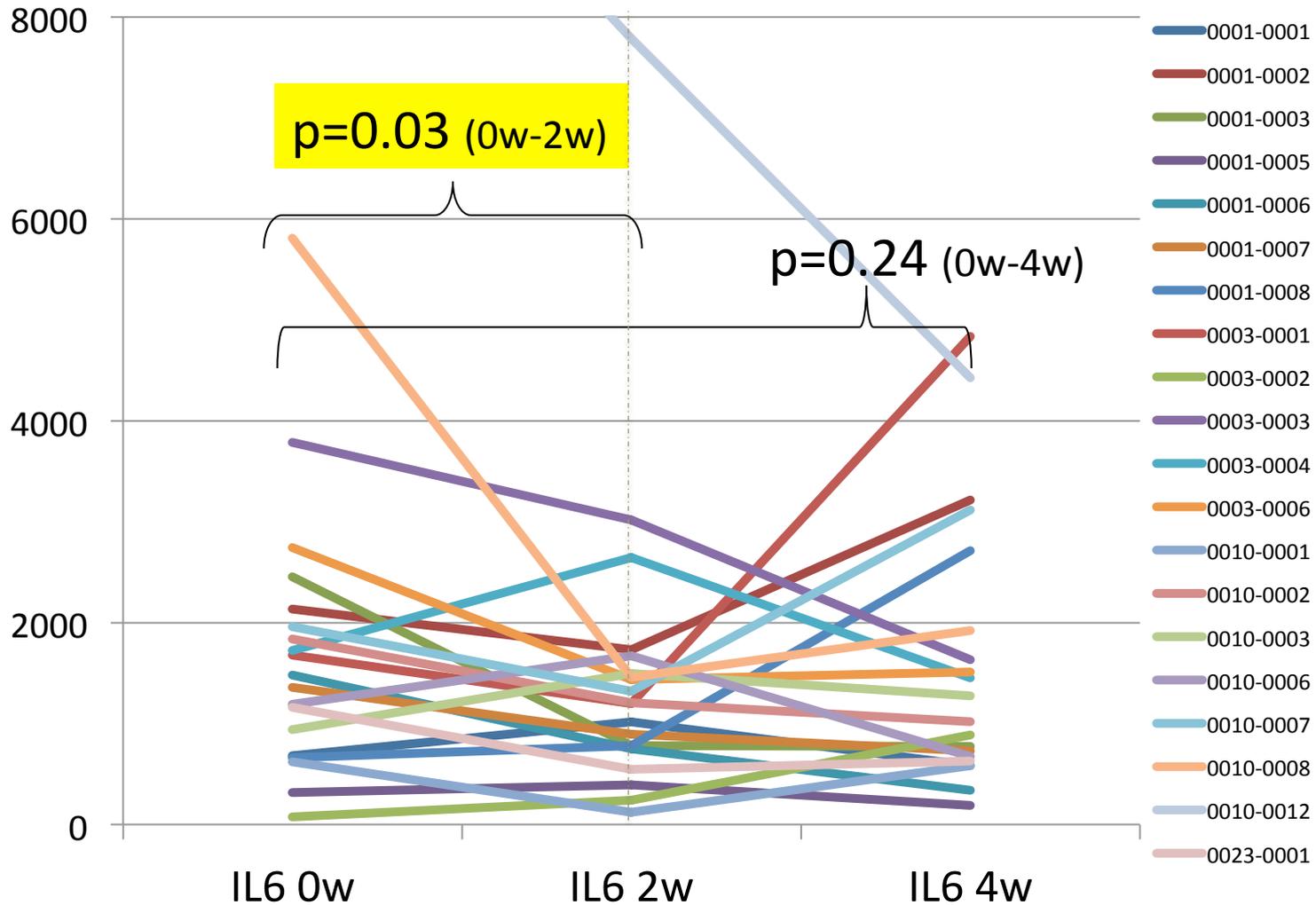
\*\*p<0.1

# <IL-1β推移:全20名>



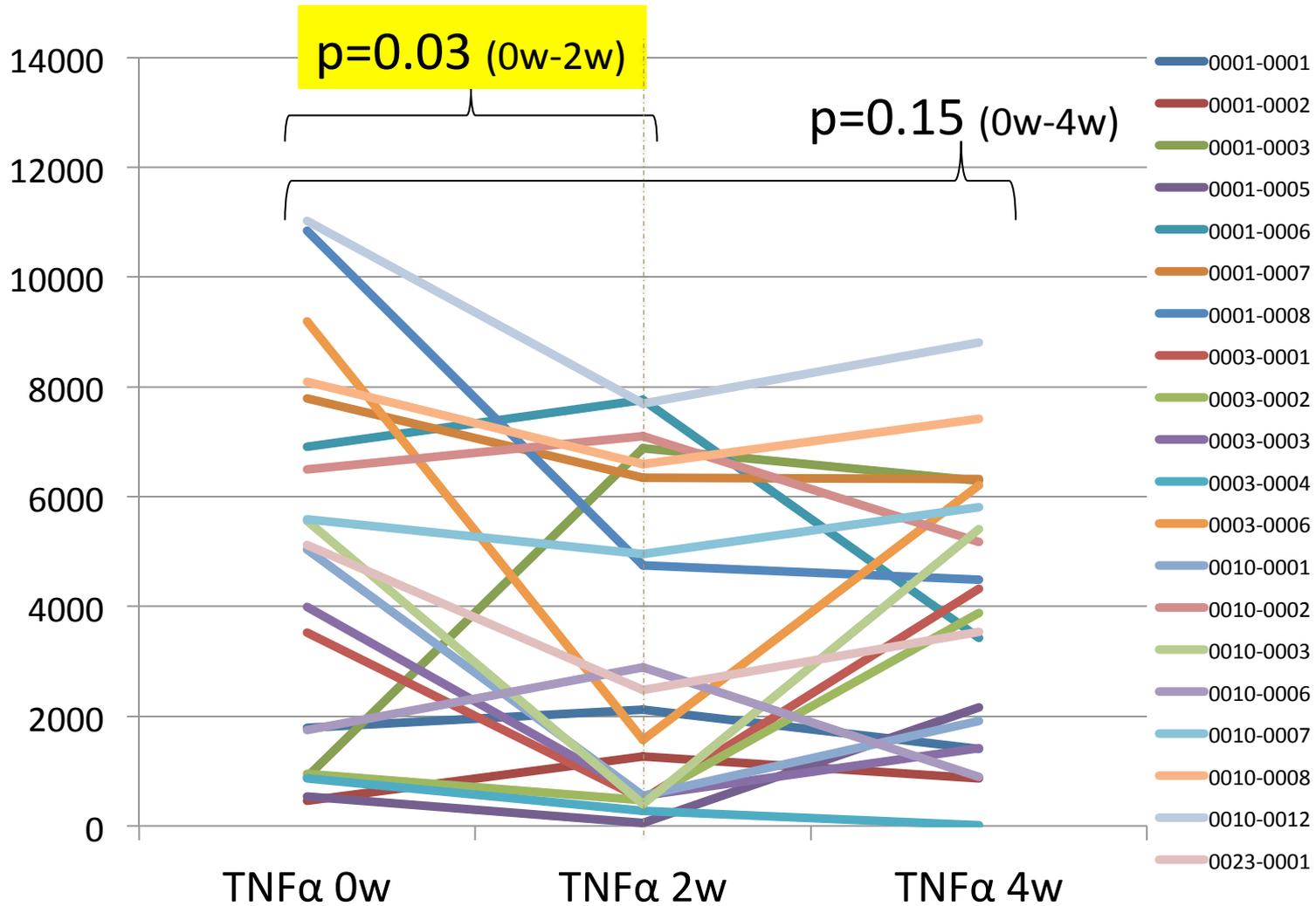
開始後2週間での「IL-1β」改善率: 75% (15/20人)  
※統計学的有意差あり!

# <IL-6推移:全20名>



開始後2週間での「IL-6」改善率: 65% (13/20人)  
※統計学的有意差あり!

# < TNF $\alpha$ 推移: 全20名 >



開始後2週間での「TNF $\alpha$ 」改善率: 70% (14/20人)  
※統計学的有意差あり!

# 結果③：EORTC QLQ-C30 推移

| N=20                                    |                            | Before          | 2w              | 4w              | p-value<br>(0w-2w) | p-value<br>(0w-4w) |
|---|----------------------------|-----------------|-----------------|-----------------|--------------------|--------------------|
| QOL<br>(higher is better)               | Global health status / QoL | 58.3<br>(±23.9) | 53.5<br>(±29.4) | 58.3<br>(±21.6) | 0.18               | 0.77               |
| Functional Scales<br>(higher is better) | Physical functioning       | 79.7 (±19.4)    | 76.8 (±23.7)    | 77.7 (±22.5)    | 0.34               | 0.43               |
|   | Role functioning           | 76.7 (±28.3)    | 76.5 (±26.4)    | 72.5 (±29.3)    | 0.78               | 0.61               |
|   | Emotional functioning      | 82.9 (±13.5)    | 78.5 (±19.7)    | 80.8 (±22.1)    | 0.45               | 0.75               |
|   | Cognitive functioning      | 83.3 (±20.2)    | 75.4 (±25.7)    | 80 (±23.3)      | 0.91               | 0.65               |
|   | Social functioning         | 86.7 (±19.2)    | 76.3 (±30.1)    | 81.7 (±24.7)    | 0.16               | 0.33               |
| Symptom Scales<br>(higher is worse)     | Fatigue                    | 35.0 (±21.1)    | 38.6 (±27.3)    | 38.6 (±24.1)    | 0.54               | 0.36               |
|   | Nausea and vomiting        | 6.7 (±11.3)     | 4.4 (±12.2)     | 8.3 (±23.9)     | 0.38               | 0.75               |
|   | Pain                       | 24.2 (±27.3)    | 20.4 (±25.9)    | 21.7 (±27.6)    | 0.21               | 0.52               |
|   | Dyspnoea                   | 20.0 (±27.4)    | 19.3 (±27.9)    | 18.3 (±27.5)    | 0.54               | 1                  |
|   | Insomnia                   | 22.8 (±33.4)    | 19.3 (±25.6)    | 21.7 (±29.1)    | 1                  | 1                  |
|   | Appetite loss              | 25.0 (±28.4)    | 29.8 (±29.2)    | 23.3 (±26.7)    | 0.48               | 0.72               |
|   | Constipation               | 13.3 (±25.1)    | 12.3 (±25.4)    | 10.0 (±24.4)    | 0.58               | 0.33               |
| Diarrhoea                               | 23.3 (±32.6)               | 26.3 (±32.5)    | 21.7 (±22.4)    | 0.63            | 0.79               |                    |

# 結 果

- CRPは約半数にて減少傾向を認めたものの、統計的に有意な変化ではなかった。
- 一方で、炎症性サイトカインであるIL-1 $\beta$ ・IL-6・TNF $\alpha$ は、当初2週間の前後比較で有意な減少を認めた。
- QOL指標に有意な変化なかった。

# 考 察

- フコイダンが、進行癌患者の炎症性サイトカインを短期間で減少させる可能性が示唆された。
- フコイダンは、進行大腸癌患者における抗がん剤の副作用の一つ、倦怠感を有意に軽減することがRCTにて示されている。ただ、その作用メカニズムは不明（Oncology Letters 2011）。
- 癌患者の倦怠感には、炎症性サイトカインが関与していることが知られている（Brain, Behavior, and Immunity 2007）。
- 抗がん剤による倦怠感の軽減メカニズムとして、フコイダンによる抗炎症作用が関与しているかもしれない。