MICROBIOTA EFFECT ON HODGKIN LYMPHOMA and NON-HODGKIN LYMPHOMA DISEASE, INTERACTION WITH IL17 and IL12

Ekin Ece GURER[1], Sevgi KALAYOGLU-BESISIK[2], Ugur SEZERMAN[3], Zerrin AKTAS[4], Fatma SAVRAN OGUZ[1], Tarik Onur TIRYAKI[5], Durdane Serap KURUCA[6], Gulsen GUNEL[4], Fatma ERDEM[6], Mustafa Oral ONCUL[7]

1.Istanbul University, Istanbul University, Istanbul Faculty of Medicine, Department of Medical Biology

2.Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Hematology

3.Acibadem University, Faculty of Medicine/ Department of Biostatistics and Medical Informatics

4.Istanbul University, Istanbul Faculty of Medicine, Department of Clinical Microbiology

5.Istanbul University, Istanbul Faculty of Medicine, of Department of Physiology

6.Eskisehir Osmangazi University, Faculty of Medicine, Department of Microbiology

7.Istanbul University, Istanbul Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology

INTRODUCTION

Impairment of the body's immune response is important in the pathogenesis of HL and NHL (1).

IL-17 is a proinflammatory cytokine and is important in defense against infection and disease. It is secreted by immu and non-immune cells. IL-12 is a regulatory cytokine between innate and adaptive immunity and is mostly secreted monocytes/macrophages and dendritic cells (2).

The colonization formed by a large number of microorganisms living in the human body is called microbiota. T relationship between the microbiota and the host depends on the enterotype (niche) present in the gut. Intesti microbiota produces short-chain fatty acids (SCFA) such as butyrate, propianate, acetate, through carbohydr fermentation (3).

AIM

Chemotherapy treatment in Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL) diseases cau gastrointestinal epithelial damage, disrupts the intestinal microbiota balance and causes dysbiosis.

In our study, it was aimed to show the effect of the damage caused by chemotherapy on the microbiota and the effec the changing microbiota flora on the course of the disease.

In addition, changes in the cytokines of interleukin 12 and 17 (IL-12, IL-17) were observed with the treatment and changing microbiota flora.

METHOD

Fifteen adult HL and 15 adult HL patients to be treated with chemotherapy were included in the study.

Stool samples were taken twice, before chemotherapy treatment and after the 3th course of treatment.

- The mean age was 37.46±11.68 years (22-62) in HL patients and 49.53±14.72 years (24-68) in NHL patients. Gender distribution in HL patients M/F: 9/6 NHL M/F: 8/7 and in the control group M/F: 17/16.
- Samples were sequenced using **Next Generation Sequencing (NGS)** method after nucleic acid isolation.
- OTU tables were prepared using **NCBI blastn version 2.0.12** according to the **NCBI** general **16S** bacterial taxonomy reference dated 10.08.2021.
- The generated **OTU** tables were calculated with **R Statistical Computer Language version 4.04** (readr, phyloseq, microbiome, vegan, descr and ggplot2 packages) to calculate Alpha diversity and their graphics were created.
- Statistical analyzes were also performed using R Statistical Computer Language version 4.0.4 and **Rstudio IDE 1.4** (tidyverse, readr, xlsx and ggplot2 packages).
- Expression of IL-12 and IL-17 cytokines was performed by **rtPCR** twice, before and after treatment.

RESULTS

In the analyses of stool samples obtained from NHL patients before and after treatment, significant changes were observed in the genera *Peptococcus* (p=0.03), *Prevotella* (p=0.03), *Roseburia* (p=0:03) and *Dorea* (p=0.008). Among these four genera, only *Provetalla* increased in the intestinal microbiota of the patients after treatment, while the others decreased. Significant changes were also observed in *Clostridia* UCG-14 genus (p=0.03), *Coprococcus* genus (p=0.01), *Romboutsia* genus (p=0.02) and *Akkermensia* genus (p=0.03) bacteria in the samples taken from HL patients before and after treatment. Of these four genera, only *Coprocccocus* genus increased in the intestinal microbiota of the patients after treatment, while the others decreased (Figure 1-A, B).

Significant changes were observed in Nitrotoluene degradation (p=0.01) and Apoptosis multiple species (p=0.01) pathways in KEGG pathway analyses performed on pre- and post-treatment samples obtained from NHL patients. Nitrotoluene degradation pathway activation decreased after treatment, while Apoptosis multiple species pathway activation increased (Figure 2).

In the analysis of IL-12 and IL-17 expression in NHL-HL patients before and after treatment, a decrease was found in both patient groups after treatment. Comparisons with controls showed a significant decrease in IL-12 and IL-17 expression after treatment (Figure 3-A, B, C).

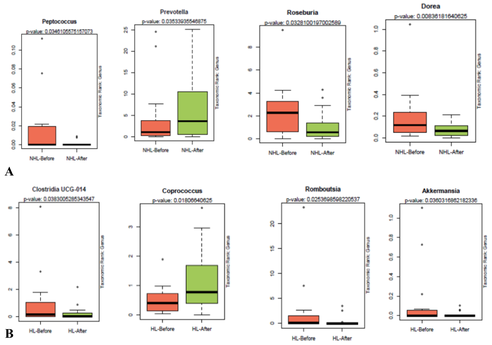


Figure 1 (A, B): Change in genera level before and after treatment

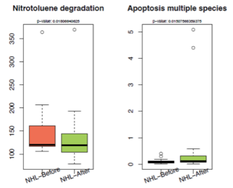


Figure 2: Change in pathway level before and after treatment

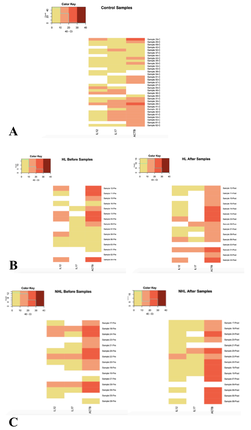


Figure 4 (A-B-C): Change in IL-12 and IL-17 cytokine levels

CONCLUSIONS

Intestinal flora monitoring after chemotherapy treatment shows that it can be a guide in the treatment of the disease. It is thought that increasing the diversity of commensal bacteria can also positively affect the prognosis of the disease.

In the future, sensitive probiotics that serve to expand the commensal flora or control the GI metabolome may be developed. Thus, these sensitive probiotics can be used as a biological switch in patients with suspected bacteraemia.

Microbiota regulated with non-pathogenic microorganisms can be used even in immunocompromised patients undergoing chemotherapy.

Dysbiosis after chemotherapy can be treated by enrichment of organisms, which is essential for the prevention of bacteraemia and sepsis.

In addition, a better understanding of the human ecosystem may allow the microbiota composition of patients to be used as a disease biomarker.

Overall, microbiota-based therapeutics hold great promise for the prevention and treatment of infections in NHL-HL patients.

Further research into the development of targeted and individualised dysbiosis prevention and treatment regimens applicable to NHL-HL patients is warranted.

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CONTACT INFORMATION

e-mail: ekinecegurer@ogr.iu.edu.tr