View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

the commercial monoclonal antibody. Collectively, we demonstrate that the rationally designed small molecules can be potent and specific drugs for anti-cancer therapy.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.006

P81

Recovery of distinct T cell subsets under severe lymphopenic conditions in hemoblastosis patients

E. Batorov[*], M. Tikhonova, I. Kryuchkova, V. Sergeevicheva, D. Batorova, S. Sizikova, G. Ushakova, A. Gilevich, A. Ostanin, E. Chernykh. *Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation* [*] Corresponding author.

Numerous studies have shown that high-dose chemotherapy and autologous hematopoietic stem cell transplantation (AHSCT) led to a profound and long-lasting state of immunodeficiency characterized by persisting low levels of T cells in hemoblastosis patients. Well-timed T-cell reconstitution is crucial for early restoration of anti-infectious and anti- tumor immune response. Lymphocyte recovery is mediated through the two main mechanisms – a homeostatic proliferation of T cells and generation of new naive T cells via thymopoiesis. It is known, that homeostatic proliferation is important for the restoration of T cell count in immune competent host during the 1st year following AHSCT. Thymus begins to fill up T cell repertoire approximately from the 6th month following AHSCT.

We have investigated dynamics of CD4+FOXP3+ Treg recovery following AHSCT and possible relationship between Tregs and clinical outcomes since the suppressive activity of Tregs under lymphopenic conditions may influence on peripheral expansion of T cells. Thymic activity following AHSCT has been evaluated by measuring amounts of CD4+ CD45RA+CD31+ naïve T cells, i.e. "recent thymic emigrants" (RTEs).109 patients with non-Hodgkin's lymphomas, Hodgkin's lymphoma and multiple myeloma underwent AHSCT in 2009–2014. The content of circulating CD4+FOXP3+ Tregs and CD4+CD45RA+CD31+ T cells was evaluated using flow cytometry before AHSCT, at the day of engraftment, and following 6 and 12 months.

Pre-transplant count of CD4+FOXP3+ Tregs was significantly higher compared to healthy controls (5.4 ± 2.9 vs 3.8 ± 1.9%; $pU = 0.011$; here and below data presented as Mean ± SD). Percentage of Tregs restored rapidly and reached initially high level at the time of engraftment, and then subsequently decreased within a year until it lowered to healthy donors' values. CD4+FOXP3+ Tregs at the time of engraftment were increased in patients with relapse or progression of disease within 6 and 12 months following AHSCT compared to non-relapsed patients (11.0 ± 6.1 vs 6.2 ± 3.0%; $pU = 0.016$, and 10.1 ± 5.2 vs 6.1 ± 3.8%; $pU = 0.008$). Pre-transplant count of CD4+CD45RA+CD31+ T cells was significantly lower compared to healthy controls (17.1 ± 11.4 vs 30.3 ± 11.2%, $pU = 0.0005$) and did not reach donors' values following 12 month (23.1 ± 13.5%, $pU = 0.032$). Relapsed patients had the same quantity of RTEs as the patients with remission within the 1st year following AHSCT. There was no any significant association between RTEs and Tregs counts.

Surprisingly, we have found high levels of circulating CD4+CD45RA- T cells co-expressing CD31 molecule in patients before AHSCT, since this molecule is infrequent on memory subsets in healthy controls (20.7 ± 12.0 vs 8.2 ± 2.1%,$pU < 0.00001$). Relative amount of CD4+CD45RA-CD31+ T cells highly correlated with CD4+CD45RO+CD31+ population (rS=0.72; $p < 0.00001$). The count of CD4+CD45RA-CD31+ T cells recovered intensively and reached the pre-transplant level within the 1st month following AHSCT, and remained at the same level throughout the follow-up. There were no any differences in relative count of CD4+CD45RA-CD31+ T cells between patients with early relapse and remission during the 1st post-transplant year.

Our data of Tregs reconstitution may confirm the earlier assumption that the presence of Tregs during the period of immune recovery preserves optimal T cell receptors diversity. However, the excess of these cells leads to the inhibition of proliferative activity and immune response and is associated with early relapse. Conversely, relatively slow recovery of RTEs determines theirlack of influence on survival within the 1st post-transplant year.

The biological role and the way of appearance of CD31 molecule on T cell memory subset (CD4+CD45RA- and/or CD4+CD45RO+) still remain unclear. Further studies are required to enlighten the role of CD31+ memory T cells on lymphoproliferative disorders pathogenesis.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.007

P57

The first Siberian experience of gastric cancer riskometry: Prospective "case-control" study

A. Belkovets[a,*], S. Kurilovich[a,b], O. Reshetnikov[a], Y. Ragino[a], M. Voevoda[a,b]. [a] *Federal State Budgetary Scientific Institution "Institute of Internal and Preventive Medicine", Novosibirsk, Russian Federation,* [b] *Novosibirsk State Medical University, Russian Federation* [*] Corresponding author.

Background: Gastric cancer (GC) remains one of the most important gastrointestinal cancers worldwide. The incidence and mortality rate from GC in Russia is higher in comparison with other European countries and USA. It should be noted that riskometry for the GC doesn't exist. Parallel assessment of pepsinogen I (PG I), pepsinogen II (PG II), PG I/PG II ratio and gastrin-17 (G-17), as well as antibodies to *Helicobacter pylori* is an exact and validated set of stomach-specific biomarkers that reflect the extent and grade of gastric atrophy as a main premalignant condition for GC.

Aim: To study the diagnostic and predicting value of biomarkers of atrophic gastritis (AG) in retro-prospective cohort case-control study in Siberian population.

Object and methods: General population sample was surveyed in Novosibirsk in 2003–2005 (10.000 subjects aged 45–69 years). Each serum sample was deeply frozen and stored. In 2008 and

2012 this database was compared with the data of the Population Cancer Registry. As a result of cross-sectional analysis of two databases 60 novel cases of GC were identified until 2011. For each case of GC, an appropriate control case was selected at the ratio 1:2 matching the area of residence, sex and age. Finally, 156 serum samples (52 – GC group and 104 – control group) were available for the analysis using a panel of serum biomarkers “Gastropanel” (Biohit, Finland). Criteria for “Gastropanel” in the diagnosis of AG were used: PG I <30μg/l, PG II <3μg/l, the ratio PG I/PG II <3, the level of basal G-17<1 pmol/l, and the presence of antibodies to *H. pylori*.

Results: Mean level of biomarkers did not differ between those with, and without GC, with the exception for PG I/PGII ratio, which was significantly lower in GC group. Indicators of gastric atrophy (OR; 95% CI) were associated with GC for PG I (2.9; 1.3–6.4), PG II (9.0; 1.8–44.3), and PG I/PG II (3.3; 1.5–7.3), but neither for G-17 (0.7, 0.4–1.6), nor for the presence of antibodies to *H. pylori* (0.4; 0.1–1.3). Multivariate regression analysis including sex, age of the patients, all biomarkers of “Gastropanel” confirmed PG I and PGI/PGII ratio as the most powerful indicators in the model. Atrophy Index (AI) was calculated as a sum of abnormal parameters of gastric atrophy (PG I, PG I/PG II ratio and G-17, see Table, $^{*}p < 0.019$; $^{**}p < 0.006$). AI 3 (all biomarkers below normal range) was more common in GC patients than in controls.

Groups	Severity of atrophy (Atrophy Index score) (%)			
	3	2	1	0
Gastric cancer	14.0**	20.0	10.0	56.0
Control	2.2	10.8	11.8	75.3*

Conclusion: As a first step in the development of GC riskometry was found that noninvasive set of serological biomarkers is an informative and non-expensive tool for the early detection of GC in population-based retrospective cohort survey in Siberian population. Low levels of PGI and PGI/PGII ratio were proven as the most valuable prognostic factors. The low level of G-17 as a single index did not significantly predict the risk of GC.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.008

P113

The protective effect of G1958A SNP on the MTHFD1 gene in susceptibility to non-Hodgkin malignant lymphomas

O. Berezina[a,*], A. Shadrina[b], E. Voropaeva[c], T. Pospelova[a], M. Filipenko[b]. [a] *Novosibirsk State Medical University, Russian Federation,* [b] *Research Institute of Chemical Biology and Fundamental Medicine SB RAS, Novosibirsk, Russian Federation,* [c] *Research Institute of Therapy and Preventive Medicine, Novosibirsk, Russian Federation*
[*] Corresponding author.

Background: Methylation systems in the cells play an important role in the metabolic processes such as purine nucleotide biosynthesis and gene and protein activity regulation. An imbalance between entities in folic acid metabolism can adversely affect nucleotide synthesis and the DNA repair and methylation system, which can cause genome instability and impairments in chromosome segregation, and lead to abnormal expression of proto-oncogenes and inactivation of tumor suppressor genes. These processes may underlie the development of a range of cancer disease, including Non-Hodgkin’s lymphomas (NHL). Quite a few studies investigating the association of SNPs in the folate-metabolizing genes with NHL risk in populations of different ethnic origin are available to date. Because the low prevalence of this disease makes sampling difficult, most of these studies have small sizes, which may be one of the reasons why results obtained are often conflicting.

The aim of this study was to investigate the role of some SNPs in folate genes (the C677T and A1298C SNPs in the MTHFR gene, A2756G in MTR, A66G in SHMT1, G1958A in MTHFD1 and 844ins68 in CBS) in genetic susceptibility to non-Hodgkin’s malignant lymphoma in the west-Siberian region.

Methods: 146 unrelated patients from the Haematological Center (Novosibirsk city) with various types of NHL were investigated. Genomic DNA was isolated from leukocytes in venous blood and from buccal epithelium, using the standard methods of DNA separation. A PCR-restriction fragment length polymorphism (RFLP) assay was used to detect the MTHFD1 G1958A and CBS 844ins68 SNPs. Genotyping of the MTHFR, MTR, MTRR and SHMT1 gene SNPs was carried out by real-time PCR allelic discrimination with TaqMan probes. The alleles and genotypes distribution of SNPs in patients were compared with their distribution in healthy white Russian subjects from Novosibirsk.

Results: We determined the allele and genotype frequencies for seven SNPs in folate metabolism in NHL and control groups. For all these SNPs, the genotype frequencies were in Hardy–Weinberg equilibrium in the control group. There were no statistically significant differences in the frequencies of alleles and genotypes of polymorphic loci of MTHFR, MTRR, CBS, SHMT1 genes between patients with NHL and controls. However, theG1958A MTHFD1 polymorphism showed a significant association with aggressive NHL. The 1958A allele (OR = 0.578, C.I. [0.415–0.805], $p < 0.001$) and AA MTHFD1 genotype (OR = 0.283, C.I. [0.130–0.613], $p < 0.0008$) were associated with decreased risk of aggressive lymphoma. The association between folate genes and indolent non-Hodgkin’s lymphoma was not revealed. The SNP G1958A causes the Arg653Gln substitution occurring in the formyltetrahydrofolate domain of the MTHFD enzyme. The substrate for this enzyme is tetrahydrofolate (THF). Potentially, the accumulation of THF results in an increase in 5,10-methylenetetrahydrofolate concentration, which in turn may enhance the efficiency of thymidylate synthesis and DNA methylation. Together, these processes may contribute to inhibition of malignant transformation.

Conclusion: G1958A SNP in the MTHFD1 gene contributes to susceptibility to NHL. The mutant allele and genotype determine the protective effect, probably, by affecting the concentration of intracellular folic acid metabolites.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.009