Evaluation of thrombocytosis as predictive factor in colorectal cancer

Ph.D. thesis

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INTRODUCTION

Colorectal cancer (CRC) is the second most common tumor both in men and women in Hungary. Although surgical therapy is still the cornerstone of the treatment of CRC, approximately one quarter of patients who had potentially curative resection die within 5 years following the establishment of the diagnosis.

The correlation between malignant tumors and hemostasis was recognized long time ago. Trousseau described already in 1865 that patient with malignancy have something in their blood that predisposes the patient to spontaneous thrombosis even without the presence of inflammation.

1. In patient with thrombocytosis the platelets induce tumor growth and angiogenesis via proangiogenic cytokines.
2. The platelets take part in metastatic progression by covering the circulating tumor cells and protecting them from mechanical damage and the host's immune response.
3. Thrombocytosis is a paraneoplastic phenomenon as the cytokines secreted by the tumor induce thrombopoiesis.

If all three hypotheses are true a vicious circle will develop. The tumor increases the platelet count that induces tumor growth, angiogenesis and metastasis formation. The whole process further increases the platelet count.

Several cytokines affecting thrombopoiesis are elevated in patients with malignant disease. Although, megakaryopoiesis is regulated at multiple points, the most frequently examined and most known regulating factor is thrombopoietin (TPO). Elevated TPO level was found in hepatoblastoma, hepatocellular carcinoma, ovarian cancer and CRC. In addition to TPO other cytokines play also a role in stimulating the megakaryopoiesis.

In addition to TPO other cytokines play also a role in the growth of megakaryocytes and the stimulation of platelet development. The most widely known are IL-1, IL-3, IL-6, IL-11, leukemia inhibiting factor and fibroblast growth factor (FGF). In addition to TPO Stone et al found correlation between thrombocytosis and IL-6 in patients with ovarian cancer. They raised the possibility of a paraneoplastic pathway; ovarian cancer raises the IL-6 level that stimulates TPO production in the liver that induces megakaryocytes in the bone marrow. The process leads to thrombocytosis.

The adhesion of platelets to the tumor cells has been confirmed. The adhered platelets protect the tumor cells from the natural killer cells (NK-cells) by expressing immunomodulating proteins on their surface such as the glucocorticoid-induced TNF-related protein (GITR) that acts as an inhibiting receptor on the NK-cells. Thus, platelets carrying the GITR ligand can protect the tumor cells. Furthermore, platelets express high number of major histocompatibility complex class I (MHC I) molecules. Thus, platelets adhered to the tumor cells show false phenotype impairing the recognition of the tumor cells.

During metastatization the tumor cells have to bind to the endothelial cells in order extravasation takes place. As shearing acts opposing adhesion, circulating tumor cells have to slow down at first. Stress caused by shearing forces is a well-known factor of platelet activation that greatly induces the adhesion of tumor cells to the platelets. The adhesion develops between glycoprotein IIb/IIIa (GPIIb/IIIa) on the platelets and the integrins on the tumor cells. Experiments show that activated platelets bound to tumor cells slow down and this promotes their binding to the endothelial cells.

Metastatization could be decreased by the inhibition of platelet activation in several tumors. Thrombocyte-deficient, knockout NF-E2 (transcriptional factor required to the platelet development from megakaryocytes) mices are protected against hematogeneous metastases. Furthermore, platelet depletion caused by anti-thrombocyte serum decreases the incidence of pulmonary metastases in CRC.

Angiogenesis is essential in the metastatization. Tumor vessels have different structure than normal microcapillaries because their pericyte cover is often deficient, the basal membrane around the endothelial cells can be damaged that facilitates the entry of tumor cells in the vessels.

Platelets activated by the endothelial damage secrete hundreds of proteins from the α- and dense granules and lysosomes. In addition to several proangiogenic cytokines antiangiogenic cytokines are released in this way as well.

Proangiogenic cytokines are vascular endothelial growth factor (VEGF), PDGF, basic fibroblast growth factor (bFGF), endothelial cell growth factor (ECGF), transforming growth factor (TGF), insulin-like growth factor (ILGF), angiopoietin-1, sphingosin-1-phosphate, matrix metalloproteases (MMP).

Antiangiogenic cytokines released from platelets are thrombospondin-1, plasminogen activator inhibitor 1 (PAI-1) and angiostatin. Substances inhibiting the angiogenesis counteract the activity of proangiogenic factors, thus, platelets are able to both inhibit and stimulate angiogenesis.

The pro- and antiangiogenic factors are stored differently in the various subpopulation of the α-granules of the platelets and they can be selectively secreted on the binding of specific receptors on the surface of the platelet. In addition to the paracrine effect of the platelet-derived growth factors it has also been proven that platelets have also a direct role in the stimulation of angiogenesis. Platelet residues and microparticles have been found in the newly-formed vessels and in vitro data showed straightforward dose-response relationship between platelet count and the intensity of neoangiogenesis. Platelets promote the migration and adhesion of bone marrow-derived cells to the place of angiogenesis and the differentiation of endothelial progenitors to mature endothelial cells. Furthermore, activated platelets play a role in the vascular homeostasis of tumors by secreting their granules and preventing hemorrhage in tumors. That is an essential step in the tumor microenvironment as the

tumorous angiogenesis is characterized by morphologically abnormal, immature, dilated and leaking vessels.

AIMS OF THE STUDY

I evaluated the predictive role of thrombocytosis in colorectal cancer and in the liver metastasis of colorectal cancer (mCRC) (1), I studied thrombocytosis accompanying tumors depending on the presence of the primary tumor (2) and I searched for other factors that influence the extent of thrombocytosis (3).

In retrospective studies I looked for the answer for the following specific questions:

1. Regarding the predictive value of paraneoplastic thrombocytosis:
    - 1.1 Is preoperative thrombocytosis a useful predictive factor in colorectal cancer with different stages and in colorectal liver metastasis?
    - 1.2 Is platelet/lymphocyte ratio a more reliable prognostic factor in colorectal cancer and in colorectal liver metastasis than plain platelet count?
    - 1.3 What is the correlation between the platelet/lymphocyte ratio and cancer-specific survival (CSS) and disease-free survival of

patients with colorectal cancer and colorectal liver metastasis?

2. Regarding thrombocytosis depending on the presence of the primary tumor:

2.1 Does the platelet count change following the resection of the primary colorectal cancer?

2.2 What is the tendency of postoperative platelet count over time?

2.3 Is postoperative platelet count predictive regarding tumor and metastatic progression?

3. Other factors influencing tumor-related thrombocytosis

3.1 Do gender, tumor size, presence of distant metastasis, stage or localization influence the extent of tumor-related thrombocytosis?

MATERIALS AND METHODS

In the first part of my study I evaluated the predictive value of thrombocytosis and platelet/lymphocyte ratio. Retrospectively I analyzed the clinical data of 357 patients with primary colorectal cancer (CRC) of different stages and of 128 patients with colorectal liver metastasis (mCRC) who underwent surgery between 2001 and 2011 in Uzsoki Hospital.

Patients in the mCRC group were independent from those in the CRC group. One of the inclusion criteria was successful (R0) resection. In the mCRC group the number and size of metastases were not handled distinctively. Exclusion criteria were as follows: other

synchronous tumor outside the colon and rectum, inflammatory disorders (insufficient anastomosis, pneumonia, inflammation of the wound, abscess, cholecystitis, Crohn's disease, ulcerative colitis), non-curative resection and steroid therapy. A total of 31 patients were excluded, thus clinical data of 336 CRC patients of diverse stages and 118 mCRC patients were evaluated.

Preoperative blood samples drawn within the shortest time prior the date of operation were analyzed. Thrombocytosis was defined as platelet count over $400x10^3/\mu L$. Patients were divided into two groups: in the first group patients had a platelet count above 400 x $10^3/\mu L$ whereas patients in the second group had a platelet count below this value. The PLR was counted as the ratio of the platelet count and the absolute lymphocyte count. A value of PLR of 300 [number of platelets per mm3 / number of lymphocytes per mm3] was used to divide patients in two risk groups. This value differs from values in literature used for other types of cancer. Overall survival (OS) of the patients starts at the date of surgery and ends at the time of death caused by the tumor. The DFS was counted as the time from the surgical intervention until the recurrence of the disease.

<u>The aim of the second part of the study was to define how the resection of the primary tumor influences the predictive value of thrombocytosis.</u>

The same exclusion criteria were used (synchronous tumor outside the colon and rectum, inflammatory disorders,

non-curative resection and steroid therapy) as in the first part of the study. In 336 patients platelet count was analyzed 1 month after the operation due to CRC. Data were collected from the routine laboratory examinations. One month was chosen to eliminate the effects of postoperative inflammations or anemia on the platelet count. None of the patients received oncologic therapy during this period. No further patient had to be excluded, therefore, the number of patients and clinicopathological data were consistent with those in the first part of the study.

RESULTS

Comparison of thrombocytosis and platelet-lymphocyte ratio as predictive factor

In the CRC group with 336 patients the distribution of men and women was nearly identical. The median age was 67 years. In this group the number of enrolled patients of different stages (stage I: 22%, stage II: 29%, stage III: 30%, stage IV: 19%) was accidentally similar. The mean overall survival was 29 months. In the mCRC group men were in majority (80/118 patients) and the average age was 61 years. The median overall survival was 24 months in this group.

Both in the CRC and the mCRC group I found that OS was significantly worse in patients who had elevated platelet count ($HR = 2.2$, $p < 0.001$ and $HR = 2.9$, $p = 0.018$).

Multivariate analysis indicated that elevated platelet count was an independent prognostic factor of cancer-specific survival (CSS; $HR = 1.7$, $p = 0.035$) and

mCRC (HR = 3.1, p = 0.017) even when adjusted for tumor stage, grade, localization and patient gender and age.

Reactive or secondary thrombocytosis can occur in several diseases; the production of platelets is increased in the bone marrow and more than normal is transferred to the circulation. It is generally accepted that the same process occurs in tumors when anemia related to the underlying malignancies induces thrombocytosis. Therefore, I also investigated the red blood cell count of the patients. According to my analysis the predictive value of thrombocytosis is independent from anemia.

The analysis also showed that the DFS was significantly worse in patients with elevated platelet count (HR = 2.0, p = 0. 011).

I found PLR to be prognostic in univariate analysis in the CRC (HR = 3.8, p < 0.001) but not in the mCRC group (HR = 0.9, p = 0.82). In the multivariate analysis the PLR was not a valuable prognostic factor in either of the two cohorts (HR = 0.92, p < 0.001 and HR = 0.89, p = 0.789 respectively).

Evaluation of paraneoplastic thrombocytosis in colorectal cancer

A total of 45 patients had preoperative thrombocytosis; consistently with the previous experience the prognosis of these patients was signicantly worse. The average overall survival was 84.4 and 27.2 months and the average follow-up time was 35.2 and 46 months in the groups below and above ULN, respectively.

The platelet count decreased considerably in most patients postoperatively; 29 patients had preoperative thrombocytosis and normal platelet count postoperatively. However, the switch from preoperative thrombocytosis to normal postoperative platelet count in these patients did not show better survival. While in half of the patients with preoperative thrombocytosis normal postoperative platelet count was noted, 24 patients with preoperative normal platelet count developed thrombocytosis 1 month after surgery. The prognosis of these patients was similarly unfavorable as of patients with preoperative thrombocytosis. Because of this increase the number of patients with pre- and postoperative thrombocytosis (40 vs. 45) has hardly changed. Therefore, it seemed to be important to evaluate the prognostic value of postoperative thrombocytosis as well. The median overall survival was 84.4 and 45.8 months and the average follow-up time was 36.5 and 44.8 months in the groups below and above ULN, respectively.

Univariate analysis showed that 1-month postoperative platelet count alone was almost significant predictive factor of patients' overall survival. In a multivariate setting, when corrected for location, stage, gender, tumor size, and controlling for age (> 65 years vs. ≤ 65 years), post-operative platelets remained a significant, independent prognostic marker (HR = 2.369, logrank P = 0.00476). Pre-operative platelets were also predictive under the same multivariate conditions (HR = 1.878, logrank P = 0.0277).

Finally, I combined the two differences and counted HR in patients with pre- and/or postoperative thrombocytosis. Thrombocytosis at any time (pre- or postoperatively) had a HR=1.97 (1.30-2.99) and a p=0.0014 and they remained predictive also with multivariate analysis (HR=1.91 (1.23-2.97), p=0.0038). This suggests that postoperative platelet count may provide extra information on the prediction of overall survival.

Additionally, both the pre- and the postoperative thrombocytosis had greater relative hazard in men than in women, although, this difference was not statistically significant (logrank test on correlation of the two genders and thrombocytosis, p=0.35 and p=0.26). It could be explained by the fact that women tend to have higher platelet count that may influence the predictive value of platelets.

I evaluated the role of tumor location regarding thrombocytosis and survival. I found significantly higher preoperative platelet count in colon tumors than in rectal tumors ($p<0.001$). Interestingly, such difference could not be observed regarding the postoperative platelet count. Furthermore, patients with rectal cancer had also a better overall survival rate (HR = 0.6, logrank p=0.037) compared to rest of the cohort.

Considering the causative relationship of the platelet count, tumor progression and metastatic progression I examined whether platelet count in the lower part of the normal range ($< 250 \times 10^3/\mu L$) is accompanied by better survival. Although, such trend could be observed

in two independent cohorts, lower platelet count did not prove to be a significant, independent prognostic factor regarding better outcome. I evaluated the HR of the lower normal range compared with the other part of the normal range: univariate analysis showed a HR=0.70 (0.44-1.12) and a p=0.134. If it was corrected for tumor stage, grade, location, gender and age, HR was 0.85 (0.51-1.41) and p value 0.54, that suggests that the better survival rate of patients in the lower range could be attributed to the stage as well.

CONCLUSIONS

1. *The results of the comparison of thrombocytosis and platelet-lymphocyte ratio as predictive factors are summarized as follows:*
    1.1. Preoperative platelet count is a valuable prognostic factor in CRC and mCRC. Platelet count in these tumors is the independent prognostic marker of OS and DFS.
    1.2. PLR shows no benefit over platelet count regarding patient's survival after the diagnosis of CRC or mCRC.
2. *During the evaluation of paraneoplastic thrombocytosis in colorectal cancer I found the following:*
    2.1. Preoperative platelet count significantly decreases compared to the postoperative count after the resection of the primary tumor. I confirmed indirectly that there is a causative correlation between the primary tumor and the platelet count.

2.2. The decrease of the postoperative platelet count can be demonstrated both in the first and the second postoperative month.
2.3. Thrombocytosis has predictive power regarding the CRC patient's survival both in the first and the second postoperative month.
2.4. In CRC both the pre- and the postoperative thrombocytosis had worse predictive power for survival in women than in men. The results raise the possible correlation of thrombocytosis and female sex hormones.
2.5. In colon-derived tumors significantly higher platelet counts can be observed than in rectal cancer. This observation reflects the different behavior of the different locations despite the fact that this difference disappears for postoperative platelet count in both cohorts.
2.6. Tumor size defining the largest extension of the tumor correlates with the preoperative platelet count. However, tumor size did not contain enough information to be a good prognostic marker.

LIST OF OWN PUBLICATIONS

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4. Valéria Jósa, Marcin Krzystanek, Aron C Eklund, Ferenc Salamon, Attila Zaránd, Zoltán Szállási, **Zsolt Baranyai**. Relationship of postoperative thrombocytosis and survival of patients with colorectal cancer. International Journal of Surgery, accepted for publication, Ms. Ref. No.: IJS-D-15-00041. **IF: 1,650**

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