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Druge kronične mijeloproliferativne bolesti

KARAKTERISTIKE BOLESNIKA SA SEKUNDARNOM ERITROCITOZOM I USPOREDBA S POLICITEMIJOM VEROM

HOLIK H.[1,2], Krečak I.[3], Coha B.[1], Vučinić Ljubičić I.[1], Kovač Peić A.[1], Rajkovača Latić I.[1], Miškić B.[1,2]

[1] Opća bolnica dr. Josip Benčević Slavonski Brod, Slavonski Brod, Hrvatska
[2] Sveučilište Josipa Jurja Strossmayera u Osijeku, Medicinski fakultet Osijek, Osijek, Hrvatska
[3] Opća bolnica Šibenik, Šibenik, Hrvatska

hholik@gmail.com

Ključne riječi: eritrocitoza, policitemija rubra vera, arterijska hipertenzija, KOPB, pušenje

Cilj: Prikazati karakteristike bolesnika sa sekundarnom eritrocitozom (SE) i usporediti ih s policitemijom verom (PV).

Metode: Retrospektivno su identificirani novodijagnosticirani bolesnici sa SE i PV u Općoj bolnici dr. Josip Benčević, Slavonski Brod. Bilježeni su klinički, demografski i laboratorijski podaci. Dijagnoza PV revidirana je prema kriterijima Svjetske zdravstvene organizacije (SZO) iz 2016., dok su kao SE definirani oni bolesnici koji su imali vrijednosti eritrocita i/ili hemoglobina iznad referentnih vrijednosti bolničkog laboratorija, a nisu zadovoljili kriterije SZO za PV. Karakteristike bolesnike uspoređene su s hi-kvadrat testom, Mann-Whitney U testom ili ANOVA testom. Statistički značajnom smatrana je p vrijednost <0.050.

Rezultati: Uključena su 66 bolesnika sa SE i 46 bolesnika s PV; nije bilo razlike u spolu (p=0.795), no bolesnici sa SE su bili značajno mlađi (53vs65god.; p<0,001). Kod bolesnika sa SE, 15 (23%) ih je imalo kroničnu opstruktivnu plućnu bolest (KOPB), 13 (20%) pušenje, a 12 (18%) srčanu bolest kao uzrok SE. Kod 26 (39%) bolesnika nije nađen uzrok SE. Od tih bolesnika, šest su bili dobrovoljni darivatelji krvi, a četiri su imala pozitivnu obiteljsku anamnezu za eritrocitozu i/ili policitemiju. U odnosu na PV, bolesnici sa SE su imali značajno niže vrijednosti eritrocita [srednja vrijednost(SV) 5,8vs6.7×1012/L; p<0.001], hemoglobina (medijan 172vs183g/L; p=0.001), hematokrita(SV 51vs55.9%; p<0.001), leukocita (medijan 8.4vs11.3×109/L; p<0.001), trombocita (SV 256vs500x109/L; p<0.001) i eritropoetina (SV 9.65vs2.16 IU/L; p=0.013), više vrijednosti serumskog željeza (medijan 19vs8.7μmol/L; p=0.028) i feritina (medijan 115vs69μg/L; p=0.017), rjeđe arterijsku hipertenziju (59vs84%; p=0.003) i preboljelu trombozu (6vs30%; p<0.001), a nijedan nije imao uvećanu slezenu (p=0.021).

Zaključak: Najčešći uzrok SE su KOPB/pušenje (43%), a potom srčana oboljenja. U odnosu na PV, bolesnici sa SE imaju značajno niži broj eritrocita, leukocita i trombocita, te nižu koncentraciju hemoglobina i hematokrita, što ukazuje na "panmijelozu" prisutnu u PV. S druge strane, niže vrijednosti serumskog željeza i feritina upućuju na povećane metaboličke potrebe PV. Bolesnici sa SE su mlađi, nemaju splenomegaliju, a rijetko i raniji trombotski događaj. Očekivano, bolesnici s PV češće imaju arterijsku hipertenziju, no čini se da obje skupine bolesnika imaju veću učestalost u odnosu na opću populaciju (~45%). Dodatna obrada potrebna je kod bolesnika sa SE i pozitivnom obiteljskom anamnezom.

PLK1 AND CDC25C mRNA EXPRESSION IN PATIENTS WITH MYELOFIBROSIS ARE PROGNOSTIC OF WORSE SURVIVAL

GALUSIC D.[1], Lucijanic M.[2], Livun A.[3], Radman M.[4,5], Blaslov V.[1], Vicelic Cutura L.[1], Petric M.[1], Miljak A.[1], Lucijanic J.[6], Drmic Hofman I.[5,7], Kusec R.[2,3,8]

[1] Department of Hematology, University Hospital of Split, Split, Croatia
[2] Hematology Department, University Hospital Dubrava, Zagreb, Croatia
[3] Clinical Institute of Laboratory Diagnosis, Division of Molecular Diagnosis and Genetics, University Hospital Dubrava, Zagreb, Croatia
[4] Department of Endocrinology, University Hospital of Split, Split, Croatia
[5] School of Medicine, University of Split, Split, Croatia
[6] Health care center Zagreb-West, Zagreb, Croatia
[7] Department of Pathology, Forensic Medicine and Cytology, University Hospital of Split, Split, Croatia
[8] School of Medicine, University of Zagreb, Zagreb, Croatia

davorgalusic@net.hr

Ključne riječi: myelofibrosis; myeloproliferative neoplasm; survival; cell cycle control

Background: Polo-like-kinase-1 (PLK1) and Cell-division-cycle-25c (CDC25c) are genes coding a phosphatases which serve as a key regulators of cell division. CDC25c activation through PLK1 is required for transition from G2 to M phase of cell cycle. These genes were reported to be dysregulated in some malignant diseases, but their role in myelofibrosis has not yet been elucidated.

Methods: We have retrospectively investigated PLK1 and CDC25c mRNA expression and their clinical correlations in unfractionated bone-marrow aspirates of 43 patients with myelofibrosis (28 primary- /PMF, 15 secondary-myelofibrosis /SMF) and 12 controls.

Results: PLK1 mRNA expression did not significantly differ between PMF, SMF and controls (median ΔCT –0.58 vs –1.23 vs –0.56 for PMF, SMF and controls, respectively; P=0.103). Patients presenting with high PLK1 mRNA expression had statistically significantly inferior overall survival compared to low expression group (HR=5.87; P=0.003). Median overall survival in patients with low and high PLK1 mRNA expression was 70 and 25 months respectively. CDC25c mRNA expression did not significantly differ between PMF, SMF and controls (median ΔCT 3.08 vs 2.86 vs 2.29 for PMF, SMF and controls, respectively; P=0.162). Patients presenting with higher CDC25c mRNA expression had statistically significantly higher white-blood-cells (P=0.017), larger liver size (P=0.022), higher absolute neutrophil (P=0.010), monocyte (P=0.050), basophil (P=0.012), and eosinophil counts (P=0.013). Patients presenting with high CDC25c mRNA expression had statistically significantly inferior overall survival compared to low expression group (HR=2.99; P=0.049). Median overall survival was not reached in patients with low and was 44 months in patients with high CDC25c mRNA expression.

Conclusion: Our data suggest that higher PLK1 and CDC25c mRNA expression are prognostic of worse survival and that CDC25c expression is associated with more proliferative phenotype of myelofibrosis. Future studies investigating these interesting associations are warranted.

MUTACIJA V617F U GENU ZA JAK2 U MIJELOPROLIFERATIVNIM NEOPLAZMAMA DIJAGNOSTICIRANIM U KLINIČKOM BOLNIČKOM CENTRU OSIJEK

GAJDAŠIĆ I.[1], Periša V.[1,2], Suver-Stević M.[3], Sinčić-Petričević J.[2]

[1] Medicinski fakultet Osijek, Osijek, Hrvatska
[2] Klinički bolnički centrar Osijek, Zavod za hematologiju, Osijek, Hrvatska
[3] Klinički bolnički centra Zavod za transfuzijsku medicinu, Osijek, Hrvatska

ivona.gajdasic@gmail.com

Ključne riječi: mutacija JAK2 V617F, mijeloproliferativne neoplazme, policitemija rubra vera, primarna mijelofibroza, esencijalna trombocitemija

Uvod: Brojnim istraživanjima mijeloproliferativnih neoplazmi (MPN); policitemiji rubra vera (PRV), esencijalnoj trombocitemiji (ET) i primarnoj mijelofibrozi (PMF) primijećena je učestalost pojavljivanja mutacije V617F u Janus kinaza 2 genu (JAK2).

Ciljevi istraživanja: Ocijeniti učestalost prisutnosti somatske mutacije V617F u JAK2 genu u skupinama oboljelih od MPN te ispitati postoji li razlika u ekspresiji mutacije između različitih podentiteta MPN.

Ispitanici i metode: Istraživanje obuhvaća 64 bolesnika s dijagnozom MPN: PV (34), ET (26) i PMF (4). DNA je izolirana iz uzoraka pune krvi. Detekcija JAK2 V617F učinjena je metodom alel specifičnog PCR.

Rezultati: Somatska mutacija V617F JAK2 gena, prisutna je kod većine ispitanika (P < 0,001), kod njih 56 (87,5 %). Pronađena je značajna povezanost između JAK2 statusa i dijagnoze ispitanika (P = 0,03). Učestalost mutacije u PMF je 100%, u PRV 97,06%, a u ET 73,08%. Trombozu je imalo 17,2% pacijenata (P < 0,001). Od toga broja 72,7 % bila je arterijska tromboza. Prosječna vrijednost značajno je veća kod ispitanika s prisutnom JAK2 mutacijom za slijedeće kliničke parametre; eritrociti, hemoglobin, hematokrit i leukociti (P < 0,05). Vrijednost Hb je značajno veća, a vrijednost LDH je značajno manja kod ispitanika s ET i prisutnim JAK statusom (P < 0,05).

Zaključak: U objavljenim studijama provedenim u Hrvatskoj i u drugim populacijama podaci za učestalost mutacije JAK2 V617F kod oboljelih od PV, ET i PMF variraju. Naši se rezultati za podtipove PV i ET nalaze u okviru raspona učestalosti mutacije prisutnog u publiciranim studijama. U PMF uključeni broj pacijenata premali je za donošenje konačnih zaključaka baziranih na statističkoj analizi.

PROTROMBOTIČKI RIZIČNI FAKTORI U BOLESNIKA S ESENCIJALNOM TROMBOCITOZOM

HORVAT I.[1], Boban A.[2,3], Zadro R.[4,5], Radić Antolic M.[1], Serventi-Seiwerth R.[2], Rončević P.[2], Radman I.[2], Sertić D.[2], Vodanović M.[2], Pulanić D.[2,3], Bašić-Kinda S.[2], Zupančić-Šalek S.[6,7], Vrhovac R.[2,3], Aurer I.[2,3], Nemet D.[8], Labar B.[9]

[1] Klinički zavod za laboratorijsku medicinu, KBC Zagreb
[2] Klinika za unutarnje bolesti, KBC Zagreb
[3] Medicinski fakultet, Sveučilište u Zagrebu
[4] Specijalna bolnica Sveta Katarina, Zagreb,
[5] Farmaceutsko-biokemijski fakultet, Sveučilište u Zagrebu, Zagreb
[7] Medicinski fakultet, Sveučilište u Osijeku
[8] Međunarodno Sveučilište Libertas
[9] Centar za ekspertnu medicinu

Email autora: ivanahorvat13@gmail.com

Ključne riječi: ET, tromboza, kardiovaskularni rizični faktori, mutacija V617F, dob

Cilj: Tijekom života 20–30% bolesnika s esencijalnom trombocitozom (ET) razvije trombozu. Pojedini rizični faktori za nastanak tromboze već su dobro poznati dok se doprinos drugih još istražuje. Cilj ovog istraživanja bio je utvrditi koliko nastanku tromboze doprinose neki od najpoznatijih rizičnih faktora u ET bolesnika poput prisutnosti jednog ili više kardiovaskularnih (KV) rizičnih faktora (hipertenzija, hiperlipidemija, dijabetes, pušenje i alkoholizam), mutacije V617F u genu JAK2, dob iznad 60 godina te prethodna tromboza.

Bolesnici i metode: U skupini od 134 ET bolesnika bilo je 94 žena i 40 muškaraca, uz medijan dobi prilikom postavljanja dijagnoze od 55 godina. Zabilježeni su svi trombotički događaji nastali prije postavljanja dijagnoze te nakon postavljanja dijagnoze (uz medijan prospektivnog praćenja bolesnika od 6,2 godine). Dokazivanje mutacije V617F izvedeno je metodom lančane reakcije polimeraze s alel-specifičnim početnicama prema metodi Baxter i sur. Lancet. 2005;365:1054–61. Coxovom regresijskom analizom ispitano je postoji li doprinos istraživanih rizičnih faktora nastanku tromboze te su rezultati prikazani kao omjer rizika (HR) i 95 % interval pouzdanosti.

Rezultati: Tromboza je nastala u 36 bolesnika (26,9%). Bolesnici koji su bili stariji od 60 godina imali su 3,01 puta veći rizik za nastanak tromboze (95% CI= 1,39-6,50, P= 0,005), dok je prethodna tromboza povećavala rizik 2,73 puta (95% CI= 1,16-6,44; P= 0,022). Prisutnost samo jednog KV rizičnog faktora pokazala se granično statistički značajna uz HR= 2,76 (95% CI= 0,96-7,92; P= 0,059). Najutjecajniji rizični faktori bili su prisutnost 2 ili više KV rizičnih faktora koji su povećavali rizik za nastanak tromboze 4,75 puta (95% CI= 1,58-14,21; P=0,005) dok su 3,06 puta veći rizik imali nosioci V617F mutacije u genu JAK2 (95% CI= 1,31-7,14; P= 0,010.)

Zaključak: Ovim istraživanjem dobili smo značajne rezultate o doprinosu ispitivanih faktora ka nastanku tromboze, te smo pokazali da osim same prisutnosti pojedinog KV rizičnog faktora trombozi značajno više doprinose prisutnost 2 ili više KV rizična faktora.

UTJECAJ HIDROKSIUREJE NA OPTEREĆENJE MUTIRANIM ALELOM JAK2V617F KOD BOLESNIKA S KRONIČNIM Ph(-) MIJELOPROLIFERATIVNIM NEOPLAZMAMA

SEDINIĆ M.[1], Lucijanić M.[1], Kušec R.[1], Mitrović Z.[1], Livun A.[2], Tupek KM.[2], Sorić E.[1], Pejša V.[1]

[1] Zavod za hematologiju, KB Dubrava, Zagreb, Hrvatska
[2] Klinički zavod za laboratorijsku dijagnostiku, KB Dubrava, Zagreb, Hrvatska

sedinicm@gmail.com

Ključne riječi: hidroksiureja, JAK2V617F, opterećenje mutiranim alelom, mijeloproliferativne neoplazme, policitemija vera

Cilj: Mutacija JAK2V617F prisutna je u gotovo svim slučajevima policitemije vere (PV) te u približno 50% slučajeva esencijalne trombocitemije (ET) i primarne mijelofibroze (PMF). Mnogo je puta istraživan učinak citoreduktivne terapije na mutirani alel JAK2V617F, prvenstveno s idejom stvaranja potecijalno korisnog biomarkera za procjenu učinka liječenja. Učinak hidroksiureje na opterećenje mutiranim alelom ostaje kontradiktoran, dok je primjena interferona i ruksolitiniba snažno povezana s redukcijom mutiranog alela.

Metode: Proveli smo retrospektivnu studiju u koju smo uključili bolesnike koji su imali barem dva puta kvantificiran JAK2V617F u razmaku od najmanje 12 mjeseci, a između dva uzorkovanja nisu primali citoreduktivnu terapiju ili su liječeni hidroksiurejom. Kriterije za uključivanje ispunilo je ukupno 68 bolesnika, u jednakom broju muškarci i žene, od čega 30 bolesnika s PV-om, 28 s ET-om i 10 s PMF-om. Bolesnike smo podijelili u dvije skupine. Prva skupina od 26 bolesnika nije liječena citoreduktivnom terapijom, ali napominjemo da su kod dijela bolesnika provođene periodičke venepunkcije. Druga skupina od 42 bolesnika liječena je hidroksiurejom, bez druge citoreduktivne terapije. Medijan praćenja bio je 28.5, odnosno 29 mjeseci. Količinu JAK2V617F alela izrazili smo kao postotak omjera mutiranog i nemutiranog oblika gena [broj kopija JAK2V617F/(broj kopija JAK2WT + broj kopija JAK2V617F)].

Rezultati: Medijan postotka promjene opterećenja mutiranim alelom u skupini bez citoreduktivne terapije bio je +14.56%, dok je u skupini liječenih hidroksiurejom bio –12.49% (p=0.005). Razlika je bila značajna i u skupini bolesnika s PV-om (p=0.003), dok skupine bolesnika s ET-om i PMF-om nisu pokazali statistički značajnu redukciju mutiranog alela (p=0.28 i p=0.84).

Zaključak: Veza između primjene hidroksiureje i JAK2V617F mutiranog alela ostaje kontroverzna. Veće opterećenje mutiranim alelom u literaturi povezano je s agresivnijim oblikom bolesti, odnosno trombotičkim i hemoragijskim komplikacijama te transformacijom bolesti. Hidroksiureja još uvijek ostaje lijek izbora kod velikog broja bolesnika. Prema našim rezultatima, određivanje postotka mutiranog alela može poslužiti kao potencijalni biomarker u procjeni učinka liječenja u skupini bolesnika s PV-om. Prema dostupnim istraživanjima, mogućnost redukcije mutiranog alela kod bolesnika s PV-om i ET-om potencijalno može smanjiti trombotičke i hemoragijske komplikacije, kao i učestalost transformacije bolesti.

REDUCED RENAL FUNCTION AS AN INDEPENDENT PREDICTOR OF THROMBOSIS AND DEATH IN MYELOFIBROSIS PATIENTS AND POTENTIAL THERAPEUTIC IMPLICATIONS

LUCIJANIĆ M.[1], Galušić D.[2], Krečak I.[3], Sedinić M.[1], Holik H.[4], Periša V.[5], Morić Perić M.[6], Zekanović I.[6], Štoos-Veić T.[1], Kušec R.[1]

[1] University Hospital Dubrava, Zagreb, Croatia
[2] University Hospital of Split, Split, Croatia
[3] General Hospital Šibenik, Šibenik, Croatia
[4] General Hospital Dr. Josip Benčević Slavonski Brod, Slavonski Brod, Croatia
[5] Osijek University Hospital, Osijek, Croatia
[6] General Hospital Zadar, Zadar, Croatia

markolucijanic@yahoo.com

Keywords: myelofibrosis; survival; thrombosis; kidney function; renal insufficiency; ruxolitinib

Aim: We aimed to assess prognostic significance of chronic kidney disease (CKD) in patients with myelofibrosis.

Methods: We retrospectively investigated a cohort of 176 myelofibrosis patients [128 primary-PMF; 48 secondary-SMF] from several hematology centers. Presence of CKD was determined in addition to other disease specific clinical characteristics.

Results: CKD was present in 26.1% of myelofibrosis patients and was significantly associated with older age (P<0.001), higher white blood cells (WBC; P=0.015) and WBC subsets [neutrophil, monocyte and basophil counts], higher platelets (P=0.001), lower albumin (P=0.018), higher serum uric acid (P=0.001), higher lactate dehydrogenase (P=0.022), and presence of cardiovascular risk factors (P=0.011). There was no significant association with driver mutations, degree of bone marrow fibrosis, PMF/SMF or dynamic international prognostic scoring system (DIPSS) risk categories (P>0.05 for all analyses). Presence of CKD was significantly associated with shorter time to arterial (HR=3.49; P=0.041) and venous thrombosis (HR=7.08; P=0.030) as well as with shorter overall survival (HR 2.08; P=0.009). In multivariate analyses, CKD (HR=1.8; P=0.014) was associated with shorter survival independently of the DIPSS (HR=2.7; P<0.001); its effect being more pronounced in lower (HR=3.56; P=0.036) than higher DIPSS risk categories (HR=2.07; P=0.023).

Conclusion: Myelofibrosis patients with CKD should be candidates for active management aimed at improvement of renal function. According to the current pool of evidence, ruxolitinib might be the first therapeutic choice, even in lower DIPSS risk categories.

PROGNOSTIC SIGNIFICANCE OF ELEVATED SERUM URIC ACID IN MYELOFIBROSIS PATIENTS

LUCIJANIĆ M.[1], Krečak I.[2], Galušić D.[3], Sedinić M.[1], Holik H.[4], Periša V.[5], Morić Perić M.[6], Zekanović I.[6], Štoos-Veić T.[1], Pejša V.[1], Kušec R.[1]

[1] University Hospital Dubrava, Zagreb, Croatia
[2] General Hospital Šibenik, Šibenik, Croatia
[3] University Hospital of Split, Split, Croatia
[4] General Hospital Dr. Josip Bencevic Slavonski Brod, Slavonski Brod, Croatia
[5] Osijek University Hospital, Osijek, Croatia
[6] General Hospital Zadar, Zadar, Croatia

markolucijanic@yahoo.com

Keywords: myelofibrosis; survival; thrombosis; uric acid; metabolism; myeloproliferative neoplasm

Aim: We aimed to assess serum uric acid (SUA) levels in patients with myelofibrosis, their relationship with clinical features of myelofibrosis and associations with thrombotic and mortality risks in subsets of patients with primary (PMF) and secondary myelofibrosis (SMF).

Methods: We have retrospectively investigated SUA in 173 patients with myelofibrosis (125 PMF; 48 SMF) and 30 controls. SUA was assessed in addition to other disease specific parameters.

Results: PMF patients had significantly higher SUA in comparison to SMF and controls. In both PMF and SMF higher SUA was significantly associated with arterial hypertension and decreased renal function. Among PMF patients, higher SUA was significantly associated with older age, larger spleen, higher white blood cells, higher lactate dehydrogenase, lower Immunoglobulin G levels, allopurinol use and non-smoking. Among SMF patients, higher SUA was associated with male sex. Higher SUA was univariately associated with shorter time-to-thrombosis (TTT; HR=5.05; P=0.006) and inferior overall-survival (OS; HR=2.22; P=0.006) in PMF patients. These associations remained statistically significant in multivariate-models for TTT (HR=4.56; P=0.024) independently of age and for OS (HR=1.8; P=0.048) independently of Dynamic-International-Prognostic-Staging-System/DIPSS (HR=3.07; P<0.001). SUA was not prognostic in SMF.

Conclusion: PMF patients present with higher SUA which is associated with features of more advanced disease and worse prognosis. Whether SUA lowering therapies might affect negative prognostic associations of SUA needs to be clarified in future studies.

RUXOLITINIB TREATMENT IMPROVES MUSCLE MASS IN PATIENTS WITH MYELOFIBROSIS

LUCIJANIĆ M.[1], Galušić D.[2], Sorić E.[1], Sedinić M.[1], Čubela M.[1], Huzjan Korunić R.[1], Pejša V.[1], Kušec R.[1]

[1] University Hospital Dubrava, Zagreb, Croatia
[2] University Hospital of Split, Split, Croatia
markolucijanic@yahoo.com

Keywords: myelofibrosis; cachexia; psoas muscle mass; prognosis; survival

Aim: We aimed to asses dynamics in psoas muscle mass in patients treated with ruxolitinib for higher risk myelofibrosis.

Methods: We investigated psoas muscles area (PMA) at vertebra L3 level from CT scans of patients with myelofibrosis that were treated with ruxolitinib due to high or intermediate-2 risk myelofibrosis. Patients were required to obtain start and 6-month CT scans to assess spleen size dynamics to be eligible for ruxolitinib reimbursement by Croatian health insurance company (HZZO). A total of 13 patients from two Croatian hematology centers with available CT data were analyzed. Psoas muscle mass dynamics were investigated during the 6-monhts period and compared to disease specific characteristics.

Results: We observed statistically significant rise in PMA during 6-month ruxolitinib treatment (median PMA 1287 vs 1365; P=0.002) with most patients experiencing a rise in psoas muscle mass and only two patients experiencing a slight decline (among them one immobile due to earlier cervical spine injury). Median PMA improvement after 6-months of ruxolitinib therapy was 6%. A total of 3/11 (23.1%) of patients experienced more than 10% improvement in PMA.

PMA improvement of 10% was associated with higher baseline hemoglobin level (median 117 vs 95 g/L; P=0.034) and lower DIPSS score (2 vs 4; P=0.019) with all patients achieving 10% PMA improvement belonging to the intermediate-2 DIPSS group (100% vs 20% of patients with and without 10% PMA improvement; P=0.018) and being non-transfusion dependent (100% vs 30% of patients with and without 10% PMA improvement; P=0.033). Improvement in PMA was significantly correlated with decline in the longest spleen diameter (Rho=–0.57; P=0.042).

PMA recovery was not significantly associated with etiology of myelofibrosis (primary vs secondary), degree of bone marrow fibrosis, JAK2 V617F status, baseline CRP, absolute lymphocyte count and albumin levels (P>0.05 for all analyses).

Conclusion: Our study is the first to provide evidence for muscle muss improvement during therapy with ruxolitinib. Patients with less advanced disease were more likely to achieve better PMA improvement favoring early start of ruxolitinib therapy. Direct mechanisms behind observed associations are yet to be established.

THE IMPACT OF BLOOD LIPIDS ON THROMBOSIS-FREE SURVIVAL IN ESSENTIAL THROMBOCYTHEMIA AND POLYCYTHEMIA VERA

KREČAK I.[1], Gverić-Krečak V.[1], Lucijanić M.[2]

[1] Department of Internal Medicine, General Hospital of Šibenik-Knin County, Šibenik, Croatia
[2] University Hospital Dubrava, Avenija Gojka Šuška 6, Zagreb, Croatia.
krecak.ivan@gmail.com

Keywords: low-density lipoprotein; thrombosis; survival; JAK2; myeloproliferative neoplasm

Aim: This study analyzed the impact of blood lipids [total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TG)] on thrombosis-free survival (TFS) in essential thrombocythemia (ET) and polycythemia vera (PV).

Methods: This was a single-center, retrospective study. Both diseases were diagnosed according to 2016 WHO criteria. ROC curves were constructed to identify optimal cut-off levels of blood lipids. TFS was measured from diagnosis until death or arterial or venous thrombosis. Survival analyses were performed using the methods of Kaplan and Meier and the Cox regression analysis.

Results: A total of 83 patients (40 ET and 43 PV) were included; median patient age was 66 years (21–92) and 56.6% were female. ROC curves identified optimal cut-off levels of TC, LDL, HDL and TG as >4.7mmol/L,

>1.8mmol/L, ≤0.9 mmol/L and ≤0.9 mmol/L, respectively. Median follow-up of all patients was 60 months (1–228). Total of 28.9% patients experienced events during the follow-up (11 deaths and 13 thromboses). In survival analyses, Kaplan-Meier curves for the cut-off levels of TC, HDL and TG demonstrated an overall comparable course (p≥0.050 for all analyses). Conversely, patients presenting with a LDL >1.8mmol/L demonstrated an inferior TFS when compared to patients with LDL ≤1.8mmol/L (HR 3.49, p=0.003). These patients were also more likely to be JAK2-mutated (p=0.042), with higher TC (p<0.001), higher C-reactive protein (p=0.042) and higher red cell distribution width (p=0.032), whereas no differences were found with respect to disease phenotype, sex, age, blood counts, prior thrombosis, statin use and the presence of splenomegaly, constitutional symptoms and cardiovascular risk (CVR) factors (p>0.050 for all analyses). Finally, the negative prognostic impact of higher LDL on TFS remained independently significant in a Cox regression model (HR 5.57; p=0.018) when adjusted for sex (HR 0.23; p=0.626), age >60 years (HR 4.90; p=0.026), JAK2 (HR 0.89; p=0.343), prior thrombosis (HR 6.15; p=0.013) and CVR factors (HR 0.02; p=0.893).

Conclusion: This study suggests that higher LDL levels are associated with inferior outcomes in ET and PV. The most appropriate LDL level for these patients seems to be ≤ 1.8mmol/L, similarly to general population whose total CVR is estimated as "high".

BENEFICIAL EFFECTS OF STATINS AND ACE INHIBITORS ON KIDNEY FUNCTION IN POLYCYTHEMIA VERA

KREČAK I.[1], Morić Perić M.[2], Zekanović I.[2], Holik H.[3,4], Coha B.[3], Gverić-Krečak V.[1], Lucijanić M.[5]

[1] Department of Internal Medicine, General Hospital of Šibenik-Knin County, Šibenik, Croatia
[2] Department of Internal Medicine, General Hospital Zadar, Zadar, Croatia
[3] Department of Internal Medicine, "Dr. Josip Benčević" General Hospital, Slavonski Brod, Croatia
[4] School of Medicine, University of Osijek, Osijek, Croatia, 5Department of Hematology, University Hospital Dubrava, Zagreb, Croatia

krecak.ivan@gmail.com

Ključne riječi: statins; ACE inhibitors; JAK2; kidney function; myeloproliferative neoplasm

Aims: Reduced kidney function is associated with worse clinical outcomes in patients with myeloproliferative neoplasms (MPN). Statins and angiotensin-converting enzyme inhibitors (ACE-i) have renoprotective properties and their pleiotropic effects might also affect the MPN clone. This study investigated whether concomitant use of statins and ACE-i might have a positive effect on estimated glomerular filtration rate (eGFR) in polycythemia vera (PV).

Methods: This multicenter retrospective study investigated effects of statins and ACE-i on 12-month eGFR dynamics in PV patients. Clinical data was recorded at diagnosis. Cardiovascular risk (CVR) factors were defined as presence of arterial hypertension and/or diabetes. Kidney function was estimated using the Modification of Diet in Renal Disease formula. Chronic kidney disease (CKD) was defined as eGFR<60 mL/min/1.73m2 for ≥3 months. The chi-square, the Mann-Whitney U and the ANOVA test were used to compare the clinical and laboratory characteristics between the patient groups. Multiple regression was perfomed to analyze factors associated with improvements in eGFR ≥10% at 12 months.

Results: A total of 98 JAK2-positive PV patients were included; median age was 68 years, with 48% females. Median eGFR was 71.4 (28.6–153.2 mL/min/1.73m2) and 26.5% patients had CKD. Twenty-five (25.5%) and 32 (32.7%) patients used statins and ACE-i, respectively. Patient groups were well balanced, with no differences according to sex, age, baseline eGFR, blood cell counts, high-risk disease, palpable splenomegaly, frequency of CKD, and hydroxycarbamide use. However, statin-users more often had prior thrombosis (48% vs. 24.7%; p=0.029). Expectedly, both statin – and ACE-i users were also more likely to have CVR factors (p=0.004 and p<0.001, respectively). A total of 24% of patients had an increase in eGFR ≥10%, with a higher proportion of statin – (55.6% vs. 14%; p<0.001) and ACE-i users (61.1% vs. 12.3%; p<0.001). Statins (p=0.039), ACE-i (p=0.002) and the absence of CVR factors (p=0.037) remained independently associated with improvements in eGFR in the multiple regression model also including hydroxyurea (p=0.314), high-risk disease (p=0.510), baseline eGFR (p=0.886) and hematocrit (p=0.086).

Conclusion: Both statins and ACE-i might have renoprotective properties in PV. Further studies are needed to elucidate whether the use of these drugs could also affect other MPN-related outcomes.

CLINICAL OUTCOMES ASSOCIATED WITH BASELINE PLATELET COUNT IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA

LUCIJANIĆ M., Sorić E., Sedinić M., Kušec R.

Klinička bolnica Dubrava, Zagreb, Hrvatska
markolucijanic@yahoo.com

Keywords: essential thrombocythemia, leukocytosis, thrombosis, bleeding, survival

Aim: To assess relationship of baseline platelet count with clinical outcomes in our cohort of essential thrombocythemia (ET) patients.

Methods: We retrospectively investigated single institution registry of ET patients from University Hospital Dubrava. We assessed platelet count at the time of diagnosis/referral and associated clinical correlations. Patients were stratified by classical two-tiered risk stratification system (age >60 years or history of thrombosis representing high risk).

Results: We analyzed a total of 132 patients with ET. Majority of patients were female [82/132 (62.1%)]. Median age was 63 years, interquartile range 49–73 years. A total of 81/132 (61.4%) patients had high thrombotic risk. Median follow-up of our cohort was 56 months.

Median platelet count at the time of diagnosis was 746 x10^9/L, interquartile range (600–951). Baseline platelet count did not significantly differ between high and low risk patients, male and female patients nor correlated with age (P>0.05 for all analyses).

We could not establish an optimal cut-off point to discriminate thrombotic risk in the whole cohort of patients. Platelet count <600 which was proposed by some earlier studies had no significant association with time to thrombosis. However, baseline platelets <600 were significantly associated with higher thrombotic risk among patients without leukocytosis (WBC <11 x10^9/L; 105 patients); HR=6.87, P=0.009, and had no significant association with thrombotic risk among patients with leukocytosis (26 patients). Accordingly, patients with platelet count >653 (defined by the ROC curve analysis) had nearly significant association with higher bleeding risk; HR=4.75; P=0.097.

Patients with baseline platelet count >790 (defined by ROC curve analysis) had significantly shorter overall survival; HR=3.62, P=0.001, phenomenon more pronounced in patients with leukocytosis; HR=8.1, P=0.003, but also evident in patients without leukocytosis as well; HR=2.29, P=0.053. Shorter survival with platelets >790 was also pronounced among high risk patients; HR=3.53, P=0.001, but not evident among low-risk patients.

Conclusion: ET patients with higher platelet count at baseline seem to have lower thrombotic risk in the absence of leukocytosis but might be more prone to bleeding. High baseline platelets are associated with higher mortality, which might not be directly related to thrombotic and bleeding risks and deserves further studies.

PRIKAZ PACIJENTICE SA SUSTAVNOM MASTOCITOZOM PRVOTNO LIJEČENOM KAO METASTATSKI KARCINOM DOJKE

MRĐENOVIĆ S., Periša V., Marković M., Mjeda D., Kotris A., Vidić A., Sinčić-Petričević J.

Zavod za Hematologiju, Klinički Bolnički Centar Osijek, Osijek, Hrvatska
mrdenovic@gmail.com

Ključne riječi: sustavna mastocitoza, karcinom dojke, trombocitopenija, kladribin, pegilirani interferon

Mastocitoza je grupa heterogenih poremećaja koji su posljedica klonalne proliferacije abnormalnih mastocita i njihove akumulacije. Sustavnu mastocitozu odlikuje infiltracija jednoga ili više organa mastocitima. Prikazujemo slučaj pacijentice kojoj je u 02/2008. utvrđena dijagnoza adenokarcinoma lijeve dojke. Učinjena totalna mastektomija uz evakuaciju te provedena adjuvantna hormonska terapija. CT obradom u 09/2018. opisani difuzno brojni uvećani limfni čvorovi abdomena te osteolitičke i osteoblastičke promjene koštanih struktura svih trupova kralježnice, kostiju zdjelice i rebara. Promjene shvaćene u smislu metastaza karcinoma dojke te odlučeno za nastavak liječenja ribociklibom uz letrizol. Nakon IV ciklusa liječenja kontrolnom CT obradom prati se

progresija abdominalne limfadenopatije, te pojava hepatosplenomegalije i ascitesa. Pacijentica zbog progresije trombocitopenije upućena na pregled hematologa kada se uočava i leukocitoza uz monocitozu te periferna limfadenopatija. Citološkom punkcijom čvora suspektni elementi ekstramedularne hematopoeze te se učini ekstirpacija navedenog čvora i biopsija kosti. U međuvremenu kod pacijentice brzo dolazi do razvoja jetrene lezije uz hipoalbuminemiju, opsežan ascites i pleuralne izljeve i potrebu za tjednom evakuacijom 10 litara ascitesa, progresiju trombocitopenije, razvoj periorbitalnih edema, eritematoznih promjena kože lica i trupa uz svrbež, povišenu tjelesnu temperaturu i tešku malignu kaheksiju. PHD analiza ekstirpiranog limfnoga čvora i biopsije kosti potvrdi da pacijentica nije bolovala od metastatskog karcinoma dojke već postavljena dijagnoza sustavne mastocitoze uz C nalaze infiltracije mastocitima koštane srži, jetre, slezene, crijeva limfnih čvorova, pluća, skeleta kao i simptoma aktivacije mastocita. Određena razina serumske triptaze > 125 ng/mL, IPSM Score 5. Obzirom da midostaurin nije na listi nacionalnog zdravstvanog osiguranja odlučeno za liječenje kladribinom od 5 mg/m2. Uz primjenu terapije dolazi do brze i gotovo potpune regresije simptoma. Nakon provedenih VI ciklusa postiže se parcijalna remisija bolesti. Odmah nakon ukidanje terapije ponovno dolazi do pojave simptoma aktivacije mastocita no promjene nisu zadovoljile kriterije za gubitak odgovora (LOR). Odlučeno za nastava liječenja kladribinom kroz još III ciklusa te nakon toga nastavljeno liječenje pegiliranim interferonom uz metilprednizolon u dozi od 45 ug tjedno. Ovaj slučaj ukazuje na stalnu potrebu pažljivog diferencijalno-dijagnostičkog razmatranja i patohistološke verifikacije sumnje na bolest.