ZNAČAJ SPLENEKTOMIJE U SAVREMENOM LEČENJU PRIMARNE IMUNOLOŠKE TROMBOCITOPENIJE ODRASLIH

PREGLEDNI RAD

REVIEW ARTICLE

THE CURRENT ROLE OF SPLENECTOMY IN THE TREATMENT OF ADULT PRIMARY IMMUNE THROMBOCYTOPENIA

Mirjana Mitrović[1,2], Marijana Virijević[1,2], Zlatko Pravdić[1], Nikola Pantić[1], Nikica Sabljić[1], Nada Suvajdžić Vuković[1,2]

[1] Klinika za hematologiju, Klinički centar Srbije, Beograd, Srbija

[2] Medicinski fakultet, Univerzitet u Beogradu, Srbija

[1] *Clinic of Hematology, Clinical Center of Serbia, Belgrade, Serbia*

[2] *Faculty of Medicine, University of Belgrade, Serbia*

SAŽETAK

Splenektomija predstavlja kauzalni (uzročni) način lečenja primarne imunološke trombocitopenije (engl. *immune thrombocytopenia – ITP)* kojim se postiže dugotrajan dobar terapijski odgovor (DTO) kod 50 – 80% bolesnika. Međutim, učestalost postoperativnih komplikacija, pre svega krvarenja, infekcije i tromboza, visoka je i kreće se do 30%. Takođe, rizik za nastanak kako infekcija tako i arterijskih i venskih tromboza povećan je tokom čitavog života splenektomisanih pacijenata. U eri novih medikamentoznih terapijskih modaliteta, kao što su rituksimab i agonisti trombopoetinskih receptora (engl. *thrombopoietin receptor agonist – TPO-RA)*, splenektomija se sve ređe sprovodi. U dostupnim savremenim vodičima ne postoji jasan stav o redosledu primene terapijskih modaliteta u drugoj liniji lečenja odraslih sa *ITP-om*. Naime, vodič za *ITP* Američkog udruženja hematologa iz 2019. godine u drugoj terapijskoj liniji daje prednost rituksimabu u odnosu na splenektomiju, ali ne daje prednost *TPO-RA* u odnosu na splenektomiju. Sa druge strane, vodič Međunarodne radne grupe za *ITP* iz 2019. ne daje prednost nijednom terapijskom modalitetu, uključujući splenektomiju. Zbog svega navedenog, od značaja je utvrditi koji pacijent ima visok stepen verovatnoće postizanja dugotrajnog DTO-a posle splenektomije. Iako su rezultati studija koje su analizirale prediktivne faktore za DTO posle splenektomije varijabilni, faktori poput starosti bolesnika, preoperativnog broja trombocita i destrukcije trombocita u slezini (utvrđene metodom trombocitokinetskog ispitivanja), u većini studija su identifikovani kao prediktivni. Danas se smatra da je primena splenektomije u *ITP-u* dobra terapijska mogućnost za mlađe bolesnike bez komorbiditeta koji vode aktivan život i ne žele česte lekarske kontrole ili planiraju trudnoću, a kod kojih je utvrđeno da je slezina mesto destrukcije trombocita.

Ključne reči: imunološka trombocitopenija, splenektomija, dugotrajan dobar terapijski odgovor, prediktivni faktori, komplikacije

ABSTRACT

Splenectomy is a causal therapy option for adult primary immune thrombocytopenia (ITP), which achieves a long-term good therapeutic response (GTR) in 50-80% of patients. However, the frequency of postoperative complications, primarily bleeding, infection and thrombosis, is high and ranges up to 30%. Also, the risk of infections, as well as thrombosis (arterial and venous), is increased during the entire life of a splenectomized patient. In the era of new therapeutic drug modalities, such as rituximab and thrombopoietin receptor agonists (TPO-RA), splenectomy is less and less performed. In the available guidelines, there is no clear recommendation on the order of applying second-line therapeutic modalities. Namely, in the second therapeutic line, the 2019 American Society of Hematology guidelines, give preference to rituximab over splenectomy, and TPO-RA over rituximab, but do not give preference to TPO-RA over splenectomy. On the other hand, the 2019 International Working Group for ITP guidelines, do not give preference to any therapeutic modality, including splenectomy. Because of all the above, it is important to determine which patient has a high probability of achieving long-term GTR after splenectomy. Although the results from studies that have analyzed predictive factors for GTR after splenectomy are variable, patient age, preoperative platelet count, and platelet destruction in the spleen (determined by thrombocytokinetic testing) have been identified as predictive in most studies. Today, the use of splenectomy in ITP is considered a good therapeutic option for younger patients without comorbidities, who lead an active life and do not want frequent medical check-ups or are planning a pregnancy, as well as in patients with splenic platelet sequestration.

Keywords: immune thrombocytopenia, splenectomy, long-term good therapeutic response, predictive factors, complications

Autor za korespondenciju:
Mirjana Mitrović
Klinika za hematologiju, Klinički centar Srbije
Doktora Koste Todorovića 2, 11000 Beograd, Srbija
Elektronska adresa: mirjanamitrovic777@gmail.com

Corresponding author:
Mirjana Mitrović
Clinic of Hematology, Clinical Center of Serbia
2 Doktora Koste Todorovića Street, 11000 Belgrade, Serbia
E-mail: mirjanamitrovic777@gmail.com

Primljen • *Received*: April 16, 2020; **Revidiran • *Revised*:** May 19, 2020; **Prihvaćen • *Accepted*:** May 24, 2020; *Online first*: August 30, 2020.

DOI: 10.5937/SMCLK2001058M

UVOD

Splenektomija je jedan od najstarijih načina lečenja bolesnika sa primarnom imunološkom trombocitopenijom *(ITP)* [1]. Naime, prva splenektomija kod bolesnika sa *ITP-om* izvršena je 1913, a sve do pedesetih godina 20. veka bila je jedini delotvorni terapijski modalitet [1]. Sa pojavom medikamentozne terapije, pre svega kortikosteroida, splenektomija postaje modalitet druge i treće terapijske linije u *ITP-u* [1].

Splenektomija se smatra za sada jedinim kauzalnim (uzročnim) načinom lečenja *ITP-a* i ima dvostruki efekat – istovremeno se uklanjaju i mesto razgradnje trombocita obloženih autoantitelima i glavno mesto sinteze antitrombocitnih autoantitela [1]. Stoga je splenektomija visokoefikasan terapijski modalitet kojim se postiže dugotrajan dobar terapijski odgovor (DTO) kod 50 – 80% bolesnika [1,2,3]. Međutim, u eri novih terapijskih modaliteta, pre svega rituksimaba i agonista trombopoetinskih receptora *(TPO-RA)*, splenektomija se sve ređe sprovodi. Naime, u današnje vreme se splenektomiše manje od 10% bolesnika sa *ITP-om*, dok se do pre 15 – 20 godina taj procenat kretao i do 60% [4].

Ciljevi ovog preglednog rada usmereni su na ukazivanje efikasnosti splenektomije, učestalosti komplikacija ove procedure, mogućnosti preoperativne predikcije DTO-a posle splenektomije, kao i na sumiranje savremenih preporuka.

EFIKASNOST SPLENEKTOMIJE

Sistematski pregled Kojourija i saradnika iz 2004. godine, koji je uključio bolesnike sa *ITP-om*, splenektomisane klasično i laparoskopski, pokazao je da 66% bolesnika postigne i očuva DTO (1.731 od 2.623 bolesnika u 47 publikacija), tokom prosečnog praćenja od 29 meseci (opseg 1 – 153) [2]. Sa druge strane, sistematski pregled Mikejla i saradnika iz 2009. godine, koji je uključio samo pacijente sa *ITP-om* splenektomisane laparoskopski, pokazao je da je učestalost inicijalne refraktarnosti na splenektomiju 8,2% (95% IP, 5,4 – 11,0), dok je kumulativna stopa relapsa tokom dužeg praćenja *(engl. pooled long-term relapse rate)* iznosila 43,6 na 1.000 pacijent-godina (95% CI, 28,2 – 67,2). Autori zaključuju da je procenjena učestalost neuspeha splenektomije tokom pet godina praćenja 28%. Pritom, učestalost relapsa je značajno veća tokom prve dve godine posle splenektomije (92,2%; 95% CI, 49,1 – 173,2) u poređenju sa periodom od treće do pete godine (29,2%; 95% CI, 17,3 –49,0) [3]. Autori oba sistematska pregleda ističu da je nivo kvaliteta radova o splenektomiji u *ITP-u* najčešće nizak, pre svega zbog kratkog praćenja, ali i primene različitih kriterijuma za procenu odgovora [2,3].

INTRODUCTION

Splenectomy is one of the oldest forms of treatment for patients with primary immune thrombocytopenia (ITP) [1]. The first splenectomy in a patient with ITP was performed in 1913, and all through to the 1950s it was the only effective therapeutic modality [1]. With the advent of medicamentous therapy, primarily corticosteroids, splenectomy became a second-line and third-line modality in the treatment of ITP [1].

Splenectomy is currently considered the only causal therapy option for ITP, and it has a dual effect – it simultaneously eliminates the site where thrombocytes opsonized with autoantibodies are destroyed as well as the main site where antiplatelet autoantibodies are synthesized [1]. Consequently, splenectomy is a highly effective therapeutic modality whereby a long-term good therapeutic response (GTR) is achieved in 50% - 80% of patients [1,2,3]. However, in the era of new therapeutic modalities, primarily rituximab and thrombopoietin receptor agonists (TPO-RA), splenectomy is performed less and less frequently. In fact, at present, less than 10% of patients with ITP are splenectomized, while 15 – 20 years ago that percentage went up to 60% [4].

The goals of this literature review are focused on highlighting the effectiveness of splenectomy, the frequency of complications for this procedure, the possibility of preoperative prediction of GTR upon splenectomy, as well as on summarizing contemporary recommendations.

THE EFFECTIVENESS OF SPLENECTOMY

A systematic review by Kojouri et al. from 2004, which included patients with ITP, who had undergone either classic or laparoscopic splenectomy, showed that 66% of patients achieved and maintained GTR (1,731 of 2,623 patients in 47 publications), over an average monitoring period of 29 months (scope 1 – 153) [2]. On the other hand, a systematic review by Mikhael et al. from 2009, which included only patients with ITP who had undergone laparoscopic splenectomy, showed the frequency of initial unresponsiveness to splenectomy to be 8.2% (95% CI, 5.4 – 11.0), while the pooled long-term relapse rate was 43.6 per 1,000 patient-years (95% CI, 28.2 – 67.2). The authors concluded that the estimated failure rate for splenectomy, over a five-year monitoring period, was 28%. It is important to note, however, that the relapse rate was significantly higher during the first two years upon splenectomy (92.2%; 95% CI 49.1 – 173.2) as compared to the period from year three to year five (29.2%; 95% CI, 17.3 – 49.0) [3]. The authors of both systematic overviews have stated that the quality level of the papers on splenectomy in ITP is mostly low, primarily due to a short follow-up period, but also because of the application of different criteria for response assessment [2,3].

KOMPLIKACIJE SPLENEKTOMIJE

Peri i postoperativne komplikacije splenektomije se dijagnostikuju kod 30% bolesnika, dok se mortalitet kreće od 3 do 17% . Najčešće komplikacije su infekcije, krvarenje i tromboembolijski događaj [1,2,3]. U velikoj američkoj retrospektivnoj analizi 9.976 odraslih bolesnika sa *ITP-om,* od kojih je 1.762 splenektomisano, kumulativna incidencija tromboza krvnih sudova trbuha u grupi splenektomisanih bolesnika sa *ITP-om* iznosila je 1,6% u odnosu na 1% kod nesplenektomisanih [4]. Takođe, tromboza dubokih vena donjih ekstremiteta *(*engl. *deep vein thrombosis – DVT)* registrovana je kod 4,3% splenektomisanih u odnosu na 1,7% nesplenektomisanih bolesnika. S obzirom da svaka hirurška intervencija predstavlja trombogeni faktor, analiza rizika ja rađena posebno za „rane" (manje od 90 dana posle splenektomije) i za „kasne" (više od 90 dana) tromboze. Pokazano je da je splenektomija bila faktor rizika za nastanak „ranih" (HR 5,4; 95% IP, 2,3 – 12,5) ali ne i „kasnih" abdominalnih tromboza (HR 1,4; 95% IP, 0,9 – 2,6). Sa druge strane, pokazano je da splenektomija predstavlja faktor rizika i za nastanak „ranih" (HR 5,2; 95% IP, 3,2 – 8,5) i „kasnih" *DVT-ova* (HR 2,7; 95% IP, 1,9 – 3,8) [4]. U nekoliko studija je uočena povećana učestalost arterijskih tromboza u vidu cerebrovaskularnog insulta (CVI) i akutnog infarkta miokarda (AIM) kod splenektomisanih bolesnika sa *ITP-om* [5,6].

U studiji Bojla i saradnika, kumulativna incidencija sepse kod splenektomisanih bolesnika sa *ITP-om* iznosila je 11,1% u odnosu na 10,1% kod nesplenektomisanih. Splenektomija je predstavljala faktor rizika za rani i kasni nastanak sepse (HR 3,3; 95% IP, 2,4 – 4,6) [4].

Prema studiji Vijanelija i saradnika, hemoragijske komplikacije splenektomije su registrovane kod 25% bolesnika u toku splenektomije, pri čemu je 8% bilo životno ugrožavajuće [5].

PREDIKTIVNI FAKTORI ZA ISHOD SPLENEKTOMIJE

Imajući u vidu da je stopa dugotrajnog DTO-a posle splenektomije visoka, ali i da je splenektomija praćena visokom učestalošću komplikacija, od izuzetnog je značaja utvrđivanje parametara koji bi omogućili identifikaciju bolesnika sa većom verovatnoćom postizanja DTO-a i manjom verovatnoćom od nastanka komplikacija.

U literaturi je, kao potencijalno prediktivno za DTO posle splenektomije, do sada identifikovano najmanje 25 parametara [1,2]. Najčešće su ispitivani: starost, pol, prisustvo antitrombocitnih i antinuklearnih antitela, dužina bolesti pre splenektomije, odgovor

COMPLICATIONS OF SPLENECTOMY

Perioperative and postoperative complications of splenectomy are diagnosed in 30% of patients, while mortality ranges from 3 to 17 percent. The most frequent complications are infections, bleeding and a thromboembolic event [1,2,3]. In a large American retrospective analysis on 9,976 adult patients with ITP, of whom 1,762 had been splenectomized, the cumulative incidence of abdominal blood vessel thrombosis in the group of splenectomized patients with ITP amounted to 1.6%, as compared to 1% in the group of patients who had not undergone splenectomy [4]. Also, deep vein thrombosis (DVT) in the lower extremities was registered in 4.3% of splenectomized patients as compared to 1.7% of non-splenectomized patients. As every surgical procedure is a thrombogenic factor, risk analysis was performed separately for "early" (less than 90 days upon splenectomy) and for "late" (more than 90 days upon splenectomy) thromboses. It was determined that splenectomy was a risk factor for the occurrence of "early" (HR 5.4; 95% CI, 2.3 – 12.5) but not for "late" (HR 1.4; 95% CI, 0.9 – 2.6) abdominal thromboses. On the other hand, it was demonstrated that splenectomy posed a risk for the occurrence of both "early" (HR 5.2; 95% CI, 3.2 – 8.5) and "late" (HR 2.7; 95% CI, 1.9 – 3.8) DVTs [4]. Several studies found an increased rate of arterial thromboses in the form of cerebrovascular insult (CVI) and acute myocardial infarction (AMI) in splenectomized patients with ITP [5,6].

In a study by Boyle et al., the cumulative incidence of sepsis in splenectomized patients with ITP amounted to 11.1%, as compared to 10.1% in nonsplenectomized patients. Splenectomy was a risk factor for both early-onset and late-onset sepsis (HR 3.3; CI 2.4 – 4.6) [4].

According to a study by Vianelli et al., hemorrhagic complications of splenectomy were registered in 25% of patients during splenectomy, with 8% of these being life-threatening [5].

PREDICTIVE FACTORS FOR THE OUTCOME OF SPLENECTOMY

Bearing in mind that the rate of long-term GTR upon splenectomy is high, but also the fact that splenectomy is followed by a high rate of complications, it is essential to establish the parameters that would enable the identification of patients with a higher probability of achieving GTR and a lower probability of complications.

In literature, so far, at least 25 parameters have been identified as potentially predictive of GTR upon splenectomy [1,2]. The most commonly analyzed parameters are the following: age, sex, the presence of

na inicijalnu kortikosteroidnu terapiju, odgovor na ostale imunosupresive, odgovor na intravenske imunoglobuline (IVIg), broj terapijskih modaliteta pre splenektomije, inicijalni broj trombocita, broj trombocita neposredno pre i posle operacije i mesto sekvestracije trombocita [1,2]. Velika varijabilnost među studijama u pogledu kriterijuma za procenu odgovora na splenektomiju, vremena procene odgovora i dužine praćenja pacijenata uticala je da i rezultati budu varijabilni [1,2].

Faktori koji se u većini radova nisu pokazali kao prediktivni za uspešnost splenektomije su: pol, prisustvo antitrombocitnih antitela, dužina bolesti pre splenektomije, veličina slezine i odgovor na IVIg [1,2]. Sa druge strane, u velikom broju studija kao prediktivni su se pokazali: starost bolesnika, preoperativni broj trombocita i mesto destrukcije trombocita [1,2]. Postoperativni broj trombocita se pokazao kao prediktivan gotovo u svim studijama koje su ga ispitivale, ali nije utvrđena precizna granična vrednost *(*engl. *cut-off*) [1,2].

Za razliku od prediktivnih faktora za uspešnost splenektomije, daleko manji broj radova se bavio ispitivanjem prediktivnih faktora za nastanak komplikacija posle splenektomije. Među njima su studije Gonzalez-Porasa i saradnika i Parka i saradnika, koje su utvrdile da je životna dob značajni prediktivni faktor za nastanak svih vrsta komplikacija [7,8]. U studiji Bojla i saradnika, splenektomija, muški pol, starost (više od 60 godina), više od 2 komorbiditeta i nepostizanje stabilnog DTO-a bili su prediktivni za nastanak sepse [3].

SPLENEKTOMIJA, NOVI LEKOVI I NOVI VODIČI

Splenektomija je decenijama predstavljala zlatni standard druge terapijske linije bolesnika sa *ITP-om*. Njena dugotrajna efikasnost je bila značajno veća od efikasnosti dostupnih medikamentoznih modaliteta kao sto su azatioprin, mikofenolat mofetil, ciklosporin A, ciklofosfamid, danazol i dapson (Tabela 1) [1]. Međutim, uvođenjem novih efikasnih lekova kao što su rituksimab i *TPO-RA* (eltrombopag, avatrombopag, romiplostim) situacija se značajno promenila. Naime, učestalost DTO-a po primeni rituksimaba iznosi 85 – 90%, a po primeni *TPO-RA* 80% [9,10]. Međutim, posle pet godina od primene rituksimaba u remisiji se i dalje nalazi svega 20% bolesnika [9]. Sa druge strane, efekat *TPO-RA* traje dok se lekovi primenjuju. U oko 10 – 30% bolesnika po obustavi *TPO-RA* perzistira DTO [10,11].

Komplikacije tokom lečenja rituksimabom su izuzetno retke [9]. Infuziona reakcija po primeni prve doze se registruje kod 15 – 60% bolesnika i izuzetno retko je ozbiljna [9]. Hipogamaglobulinemija se

antiplatelet and antinuclear antibodies, the length of disease prior to splenectomy, response to initial corticosteroid therapy, response to other immunosuppressants, response to intravenous immunoglobulins (IVIg), the number of therapeutic modalities prior to splenectomy, the initial platelet count, platelet count immediately before and after the operation, and the platelet sequestration site [1,2]. A significant variability amongst studies regarding the criteria for assessing responses to splenectomy, the time of response assessment, and the length of patient follow-up resulted in the variability of the results [1,2].

Factors that, in most studies, did not prove to be predictive of the success of splenectomy are sex, the presence of antiplatelet antibodies, the length of disease prior to splenectomy, spleen size, and the response to IVIg [1,2]. On the other hand, in a large number of studies, the following were predictive: patient age, preoperative platelet count, and the site of platelet destruction [1,2]. The postoperative platelet count proved to be predictive in practically all the studies that analyzed it, but the precise cut-off value was not determined [1,2].

As opposed to factors predictive of the success of splenectomy, a significantly smaller number of papers analyzed the predictive factors of complications upon splenectomy. Amongst them are the studies by Gonzalez-Porras et al. and Park et al., which determined that age was a factor predictive of the development of all types of complications [7,8]. In a study by Boyle et al., splenectomy, the male sex, age (over 60 years), more than two comorbidities, and the absence of a stable GTR were predictors of sepsis [3].

SPLENECTOMY, NEW DRUGS AND NEW GUIDELINES

For decades, splenectomy was the second-line therapy gold standard for patients with ITP. Its long-term effectiveness was significantly greater than the effectiveness of available drug modalities, such as azathioprine, mycophenolate mofetil, cyclosporine A, cyclophosphamide, danazol, and dapsone (Table 1) [1]. However, with the introduction of new effective drugs, such as rituximab and TPO-RA (eltrombopag, avatrombopag, romiplostim) the situation has significantly changed. Namely, the rate of GTR upon rituximab application is 85% - 90%, and upon TPO-RA application, it is 80 percent [9,10]. However, after five years of rituximab application, only 20% of patients remain in remission [9]. On the other hand, the effect of TPO-RA lasts while the drugs are applied. In around 10 – 30% of patients GTR persists after TPO-RA is withdrawn. [10,11].

Complications during treatment with rituximab are very rare [9]. Infusion reaction upon first dose application is registered in 15 – 60% of patients and is

Tabela 1. Efiksanost i najčešće komplikacije u drugoj terapijskoj liniji bolesnika sa *ITP-om*

Lek	Procenat odgovora	Rizici/Neželjena dejstva	Cena (EUR)
Splenektomija	80% Nakon 5 – 10 godina 67%	• Rizici u vezi sa hirurgijom • Infekcije • Tromboze	/
TPO-RA Romiplostim Eltrombopag	- Nesplenektomisani 88%; - Splenektomisani 79% (dugotrajan ukoliko se lek redovno primenjuje)	• Pogoršanje trombocitopenije po obustavi leka • Retikulinska tromboza u koštanoj srži, imunogenost • Potencijalni rizik: trombotske/tromboembolijske komplikacije, progresija postojećeg hematološkog oboljenja (MDS), promene parametara krvne slike	Mesečno 1,798 – 5,450 1,043 – 3,129
Rituximab	90% (nakon 6 godina 29%)	• Rizik od potencijalno smrtnih neželjenih efekata (infuzione reakcije; teške mukokutane reakcije; progresivna multifokalna leukoencefalopatija; reaktivacija hepatitis B virusa) • Kontraindikovan kod pacijenata sa aktivnom hepatitis B virusnom infekcijom	5,275
Azatioprin	40 - 65% (dugotrajan kod 25%)	Slabost, znojenje, povišene transaminaze, neutropenija teškog stepena	Mesečno 20
Ciklofosfamid	24 - 85% (dugotrajan kod 50%)	Neutropenija, tromboza dubokih vena, nauzeja, povraćanje, rizik od sekundarnih maligniteta	Mesečno 30
Danazol	67% (dugotrajan kod 50%)	Akne, hirzutizam, povišen nivo holesterola u krvi, amenoreja, povišene transaminaze	Mesečno 30
Mikofenolat mofetil	76% (dugotrajan kod 45%)	Glavobolja, bol u leđima, abdominalna distenzija, anoreksija, nauzeja	Mesečno 30
Vinka alkaloidi	67% (dugotrajan kod 50%)	Neuropatija, neutropenija, groznica, tromboflebitisi na mestu infuzije	Mesečno 70

TPO-RA - agonisti trombopoetinskih receptora; MDS - mijelodisplastični sindrom; PML - progressive multifocal leukoencephalopathy; DVT - deep vein thrombosis.

Adaptirano iz: Suvajdžić i sar. Vodič za dijagostiku i lečenje odraslih bolesnika sa ITP-om. Aktiv za ITP, SLD. Decembar 2016 [21]

Table 1. Good therapy response and the most common side effects in second-line ITP therapy modalities

Treatment	Response rates	Risks/adverse events	Price (Eur)
Splenectomy	80% 5 – 10 years 67%	• General risks of surgery • Infection • Thrombosis	NA
TPO mimetics Romiplostim Eltrombopag	Non-splenectomized 88%; splenectomized 79% (sustained with continued administration)	• Rebound thrombocytopenia after discontinuing treatment • Increased bone marrow reticulin, immunogenicity • Hypothetical risks: thrombotic/thromboembolic complications, progression of existing haematopoietic malignancies (MDS), alterations in blood cell parameters	Per month 1,798 – 5,450 1,043 – 3,129
Rituximab	90% (6 years 29%)	• Risk of fatal adverse events (infusion reactions; severe mucocutaneous reactions; PML; hepatitis B reactivation) • Contraindicated in patients with active hepatitis B infection	5,275
Azathioprine	40 - 65% (sustained 25%)	Weakness, sweating, elevated transaminases, severe neutropenia	Per month 20
Cyclophosphamide	24 - 85% (sustained 50%)	Neutropenia, DVT, nausea, vomiting, risk of secondary malignancies	Per month 30
Danazol	67% (sustained 50%)	Acne, hirsutism, elevated cholesterol, amenorrhea, elevated transaminases	Per month 30
Mycophenolate mofetil	76% (sustained 45%)	Headache, backache, abdominal distension, anorexia, nausea.	Per month 30
Vinca alkaloids	67% (sustained 50%)	Neuropathy, neutropenia, fever, infusion site reactions	Per month 70

TPO – thrombopoietin; MDS – myelodysplastic syndrom; PML - progressive multifocal leukoencephalopathy; DVT - deep vein thrombosis; NA - non applicable.

Adapted from: Suvajdžić i sar. Vodič za dijagostiku i lečenje odraslih bolesnika sa ITP-om. Aktiv za ITP, SLD. Decembar 2016 [21]

regustruje kod 10% bolesnika i prolaznog je karaktera, dok su infekcije izuzetno retke [9]. Komplikacije tokom primene *TPO-RA* su takođe retke. Najčešća komplikacija je lezija jetre pri upotrebi eltrombopaga, koja se uočava kod 10% bolesnika i prolaznog je karaktera [10]. Učestalost arterijskog i venskog tromboembolizma tokom primene *TPO-RA* se kreće između 5,9 i 6,3% [10].

Mesto splenektomije u savremenom terapijskom algoritmu *ITP-a* odraslih je predmet žive diskusije [12,13]. Naime, vodič Američkog udruženja hematologa iz 2019. godine, u sklopu preporuka za drugu terapijsku liniju u perzistentnom ili hroničnom *ITP-u*, ne daje prednost *TPO-RA* u donosu na splenektomiju, ali im daje prednost u odnosu na rituksimab. Međutim, isti vodič daje prednost rituksimabu u odnosu na splenektomiju. Sa druge strane, vodič Međunarodne radne grupe za *ITP* iz 2019. godine, klasifikovao je sve terapijske modalitete na hirurške (splenektomija) i medikamentozne, koji su potom stratifikovani na grupu za koju postoje značajni dokazi o efikasnosti (rituksimab, *TPO-RA*) i grupu sa manje dokaza iz kvalitetnih studija (azatioprin, vinka alkaloidi, ciklofosfamid, ciklosporin, mikofenolat mofetil) [14]. Međutim, ni ovaj vodič ne favorizuje nijedan terapijski modalitet niti sugeriše redosled njihove primene. Najpreciznija preporuka za redosled primene terapijskih modaliteta u okviru druge terapijske linije za *ITP* dala je Nemačka radna grupa za *ITP* [15]. Naime, u drugoj terapijskoj liniji se preporučuju *TPO-RA* bez obzira na dužinu bolesti, odnosno njihova primena se savetuje kako u hroničnom *ITP-u* tako i u akutnom i perzistentnom *ITP-u* rezistentnom na kortikosteroide. Sa druge strane, splenektomija se preporučuje u drugoj terapijskoj liniji samo u hitnim slučajevima. Treću terapijsku liniju, prema ovom vodiču, predstavljaju splenektomija, rituksimab i ostali imunosupresivi [15].

KAKO IZABRATI IDEALNOG KANDIDATA ZA SPLENEKTOMIJU?

S obzirom da redosled terapijskih modaliteta u lečenju bolesnika sa *ITP-om* koji nisu odgovorili na kortikosteroide nije jasno definisan, postavlja se pitanje kako izabrati idealnog kandidata za splenektomiju.

Preporučuje se odlaganje splenektomije tokom prvih 12 meseci od dijagnoze bolesti zbog mogućnosti spontane remisije koje se javljaju kod 10% bolesnika bez obzira na primenjenu terapiju [1]. Prednosti splenektomije su visok stepen dugotrajnog DTO-a i niska cena same procedure [12,13]. Sa druge strane, splenektomija je trajna i ireverzibilna i praćena je doživotnim komplikacijama [12,13].

very rarely severe [9]. Hypogammaglobulinemia is registered in 10% of patients and is transient, while infections are extremely rare [9]. Complications during the application of TPO-RA are also rare. The most common complication is the occurrence of liver lesions in the application of eltrombopag, which is noted in 10% of patients, and is temporary [10]. The rate of arterial and venous thromboembolism during TPO-RA application ranges from 5.9 to 6.3% [10].

The splenectomy site in the contemporary therapeutic algorithm of adult ITP is the object of lively discussion [12, 13]. However, within the recommendations for second-line therapy in persistent or chronic ITP, the American Society of Hematology 2019 guidelines do not give priority to TPO-RA over splenectomy but do prioritize TPO-RA over rituximab. At the same time, these guidelines give priority to rituximab over splenectomy. On the other hand, the 2019 International Working Group for ITP guidelines classified all therapeutic modalities into two categories: surgical (splenectomy) and medical; these were then stratified into the group the robust evidence of effectiveness (rituximab; TPO-RA) and the group with less robust evidence from quality studies (azathioprine, vinca alkaloids, cyclophosphamide, cyclosporine, mycophenolate mofetil [14]. However, these guidelines also do not give precedence to any therapeutic modality, and they do not suggest the order of their application. The most precise recommendation for the order of therapeutic modalities within second-line therapy for ITP was given by the German Working Group for ITP [15]. Namely, regardless of the length of disease, TPO-RA are recommended as second-line therapy, i.e. their application is advised, not only in chronic ITP, but also in acute and persistent ITP resistant to corticosteroids. On the other hand, splenectomy is advised as second-line therapy only in emergencies. These guidelines recommend splenectomy, rituximab, and other immunosuppressants as third-line therapy [15].

HOW TO CHOSE THE IDEAL CANDIDATE FOR SPLENECTOMY?

Bearing in mind that the order of therapeutic modalities in the treatment of patients with ITP who have not responded to corticosteroids has not been clearly identified, the question arises as to the method of selecting the ideal candidate for splenectomy.

It is recommended to delay splenectomy during the first 12 months upon ITP diagnosis because of the possibility of spontaneous remission which occurs in 10% of patients irrespective of the applied therapy [1]. The advantages of splenectomy are the high rate of long-term GTR and the low cost of the procedure itself [12,13]. On the other hand, splenectomy is permanent and irreversible, and is followed by life-time risk of complications [12,13].

Merodavni faktori koje treba razmotriti pri odluci o splenektomiji su:

1. *Životna dob bolesnika*

Brojne studije su pokazale da je postizanje dugotrajnog DTO-a bolje kod mlađih pacijenata, a da su komplikacije ređe [1,7,8,17]. Posebnu podgrupu čine žene u reproduktivnom periodu koje planiraju trudnoću. Osim kortikosteroida i IVIg primena ostalih lekova se ne preporučuje u trudnoći, te je prihvatljiv stav o splenektomiji pre trudnoće [1,17].

2. *Komorbiditeti*

Komorbiditeti doprinose nastanku komplikacija posle splenektomije. U proceni rizika od pomoći je skala Američkog udruženja anesteziologa *(*engl. *American Society of Anesthesiologists – ASA)* koja prepoznaje pet kategorija [18]. Naime, u grupi *ASA* III, u kojoj komorbiditeti najverovatnije mogu uticati na ishod splenektomije i u kojoj je očekivana perioperativna smrtnost 1,8 – 4,3%, treba razmotriti druge terapijske modalitete [18]. Takođe, pacijenti sa visokim trombofilnim rizikom i pacijenti sa prethodnim trombozama ne smatraju se idealnim kandidatima za splenektomiju.

3. *Stil i kvalitet života bolesnika*

Bolesnici koji vode aktivan život i ne žele česte zdravstvene kontrole predstavljaju dobre kandidate za splenektomiju [1,17,19].

4. *Mesto destrukcije trombocita*

U do sada publikovanih 14 studija, koje su uključile 1.114 bolesnika sa *ITP-om* kod kojih je obavljeno trombocitokinetsko ispitivanje, pokazano je da je destrukcija u slezini prediktivna za postizanje DTO-a posle

The relevant factors that need to be considered when deciding on splenectomy are:

1. *Patient age*

Numerous studies have shown that achieving long-term GTR is better and that complications are less frequent in younger patients [1,7,8,17]. A special subgroup are women in the reproductive period who are planning pregnancy. With the exception of corticosteroids and IVIg, the application of other medication is not recommended in pregnancy, which is why the attitude on recommended splenectomy prior to pregnancy is acceptable [1,17].

2. *Comorbidities*

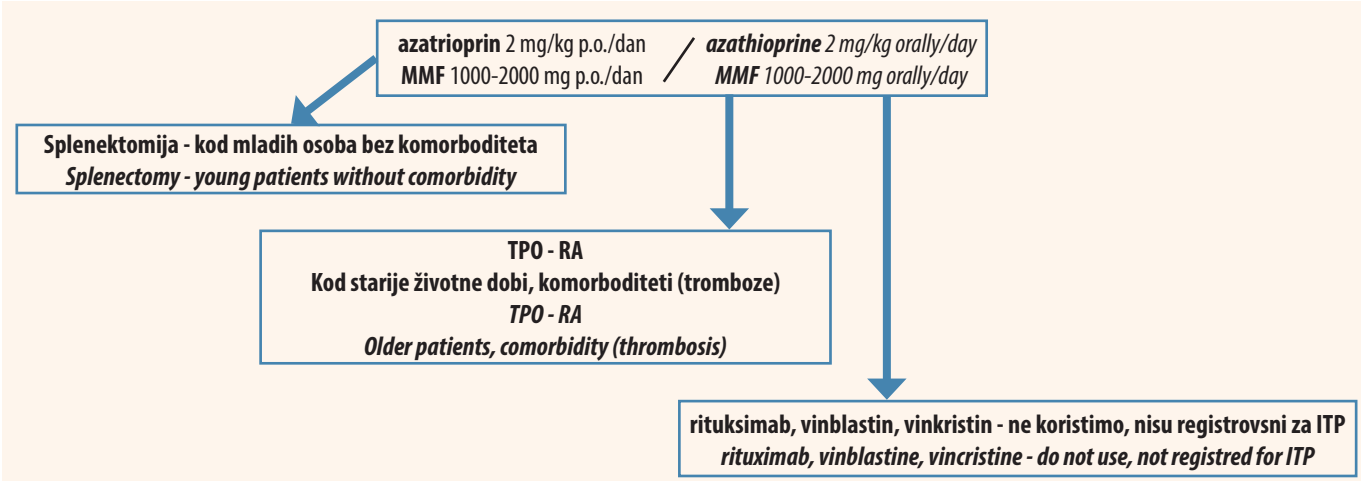
Comorbidities contribute to the development of complications upon splenectomy. The scale developed by the American Society of Anesthesiologists (ASA), which recognizes five categories, is helpful in risk assessment [18]. Namely, in the ASA III group, where comorbidities can most probably affect the outcome of splenectomy and where the expected perioperative mortality is 1.8% - 4.3%, other therapeutic modalities should be considered [18]. Also, patients with high thrombophilic risk, as well as patients with previous thromboses are considered ideal candidates for splenectomy.

3. *Patient lifestyle and quality of life*

Patients leading an active life who do not want frequent check-ups represent good candidates for splenectomy [1,17,19].

4. *Site of platelet destruction*

The 14 studies published so far, which included 1,114 patients with ITP who had undergone thrombocytokinetic testing, demonstrated the predictiveness of



Slika 1. Algoritam lečenja odraslih bolesnika sa *ITP-om* u drugoj terapijskoj liniji na Klinici za hematologiju Kliničkog centra Srbije

MMF – mikofenolat mofetil; mg – milligram; kg – kilogram; i.v. – intravenski; p.o.– peroralno; TPO-RA agonisti trombopoetinskih receptora

Adaptirano iz: Suvajdžić i sar. Vodič za dijagostiku i lečenje odraslih bolesnika sa ITP-om. Aktiv za ITP, SLD. Decembar 2016 [21]

Figure 1. Second-line therapy algorithm for adult immune thrombocytopenia patients at the Clinic of Hematology, Clinical Center of Serbia

MMF – mycophenolate mofetil; mg – milligram; kg – kilogram; i.v. – intravenous; p.o.– per os; TPO– RA thrombopoietin receptor agonist

Adapted from: Suvajdžić i sar. Vodič za dijagnostiku i lečenje odraslih bolesnika sa ITP-om. Aktiv za ITP, SLD. Decembar 2016 [21]

splenektomije u 8 od 14 studija (63,3%), a trajnog DTO-a u 7 od 11 studija (62,5%) [4,20].

5. *Dostupnost iskusnog tima*

Iako smo skloni da operativni rizik procenjujemo putem faktora vezanih za bolesnika, podjednako bitan faktor predstavlja i dostupnost obučenog hirurškog tima.

Algoritam lečenja kortikorezistentnog/kortikozavisnog bolesnika u Klinici za hematologiju KCS-a predstavljen je na Slici 1.

ZAKLJUČAK

U eri novih medikamentoznih terapijskih modaliteta, splenektomija se sprovodi sve ređe, a njena primena se najčešće odlaže dok se ne iscrpe nehirurški oblici lečenja, iako nema opšteprihvaćenog stava o redosledu primene modaliteta u okviru druge terapijske linije *ITP-a* odraslih. Međutim, splenektomija, kao visokoefikasna metoda čije se komplikacije najćešće mogu predupredi, i dalje ima svoje mesto u lečenju *ITP-a*. Idealan kandidat za splenektomiju je mlađi bolesnik, bez komorbiditeta, sa destrukcijom trombocita u slezini, koji vodi aktivan život, ne želi lekarske kontrole ili se pak radi o pacijentkinji koja planira trudnoću. U trenutku kada su dostupni mnogobrojni podjednako efikasni terapijski modaliteti, edukacija bolesnika i njegov izbor su takođe nezaobilazni faktori.

Sukob interesa: Nije prijavljen.

splenic platelet destruction for achieving GTR upon splenectomy in 8 out of 14 studies (63.3%), and for permanent GTR in 7 out of 11 studies (62.5%) [4,20].

5. *Availability of an experienced team*

Although there is a tendency to estimate the operation risk through factors related to the patient, the availability of a trained surgical team is an equally important factor.

The treatment algorithm for a corticoresistant/corticodependent patient at the Clinic of Hematology of the Clinical Center of Serbia is presented in Figure 1.

CONCLUSION

In the era of new medicamentous therapeutic modalities, splenectomy is carried out less and less frequently, and it is delayed until all non-surgical treatment options have been exhausted, although there is no generally accepted attitude on the order of applying second-line therapy in adult ITP. However, splenectomy, as a highly effective method, whose complications can most often be mitigated, still has its place in ITP treatment. An ideal candidate for splenectomy is a younger patient without comorbidities, with splenic platelet destruction who has an active lifestyle and does not want frequent check-ups; or it is a female patient planning a pregnancy. At a time when numerous and equally efficient therapeutic modalities are available, the education of the patient and their choice are also crucial factors.

Conflict of interest: None declared.

LITERATURA / *REFERENCES*

1. Mitrović M. Splenektomija u primarnoj imunološkoj trombocitopeniji: efikasnost, komplikacije i prognozni faktori povoljnog ishoda. [Subspecijalistički rad]. Beograd, Srbija: Medicinski fakultet, Univerzitet u Beogradu; 2017.
2. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood. 2004; 104(9):2623–34.
3. Mikhael J, Northridge K, Lindquist K, Kessler C, Deuson R, Danese M. Short-term and long-term failure of laparoscopic splenectomy in adult immune thrombocytopenic purpura patients: a systematic review. Am J Hematol. 2009; 84(11):743–8.
4. Boyle S, White RH, Brunson A, Wun T. Splenectomy and the incidence of venous thromboembolism and sepsis in patients with immune thrombocytopenia. Blood. 2013; 121(23):4782–90.
5. Vianelli N, Palandri F, Polverelli N, Stasi R, Joelsson J, Johansson E, et al. Splenectomy as a curative treatment for immune thrombocytopenia: a retrospective analysis of 233 patients with a minimum follow up of 10 years. Haematologica. 2013; 98(6):875–80.
6. Thai L-H, Mahévas M, Roudot-Thoraval F, Limal N, Languille L, Dumas G, et al. Long-term complications of splenectomy in adult immune thrombocytopenia. Medicine (Baltimore). 2016; 95(48):e5098.
7. Gonzalez-Porras JR, Escalante F, Pardal E, Sierra M, Garcia-Frade LJ, Redondo S, et al. Safety and efficacy of splenectomy in over 65-yrs-old patients with immune thrombocytopenia. Eur J Haematol. 2013; 91(3):236–41.
8. Park YH, Yi HG, Kim CS, Hong J, Park J, Lee JH, et al. Clinical Outcome and Predictive Factors in the Response to Splenectomy in Elderly Patients with Primary Immune Thrombocytopenia: A Multicenter Retrospective Study. Acta Haematol. 2016; 135(3):162–71.
9. Lucchini E, Zaja F, Bussel J. Rituximab in the treatment of immune thrombocytopenia: what is the role of this agent in 2019? Haematologica. 2019; 104(6):1124–35.
10. Ghanima W, Cooper N, Rodeghiero F, Godeau B, Bussel JB. Thrombopoietin receptor agonists: ten years later. Haematologica. 2019; 104(6):1112–23.
11. Mitrovic M, Elezovic I, Suvajdzic-Vukovic N. "On-demand" romiplostim therapy in immune thrombocytopenia. J Clin Pharm Ther. 2016; 41(3):351–3.
12. Browning MG, Bullen N, Nokes T, Tucker K, Coleman M. The evolving indications for splenectomy. Br J Haematol. 2017; 177(2):321–4.
13. Anguita E, Candel FJ, González-Del Castillo J, Martín-Sánchez FJ. Splenectomy in ITP: we keep removing a healthy functional organ. Ann Hematol. 2016; 95(11):1911–2.
14. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019; 3(23):3829–66.

15. Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019; 3(22):3780–817.
16. Matzdorff A, Meyer O, Ostermann H, Kiefel V, Eberl W, Kühne T, et al. Immune Thrombocytopenia - Current Diagnostics and Therapy: Recommendations of a Joint Working Group of DGHO, ÖGHO, SGH, GPOH, and DGTI. Oncol Res Treat. 2018; 41 Suppl 5:1–30.
17. Ghanima W, Godeau B, Cines DB, Bussel JB. How I treat immune thrombocytopenia: the choice between splenectomy or a medical therapy as a second-line treatment. Blood. 2012; 120(5):960–69.
18. Doyle DJ, Goyal A, Bansal P, Garmon EH. American Society of Anesthesiologists Classification (ASA Class). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
19. Suvajdzic N, Zivkovic R, Djunic I, Vidovic A, Markovic O, Marisavljevic D, et al. Health-related quality of life in adult patients with chronic immune thrombocytopenia in Serbia. Platelets. 2014; 25(6):467–69.
20. Todorović-Tirnanić MV, Obradović VB, Pavlović SV, Suvajdzić ND, Elezović IV, Colović MD, et al. 111In-platelets dynamic study in chronic immune thrombocytopenic purpura. Nucl Med Rev Cent East Eur. 2002; 5(2):121–25.
21. Suvajdžić N, Miljić P, Mitrović M. Vodič za dijagnostiku i lečenje odraslih bolesnika sa ITP-om. Aktiv za ITP, SLD. Beograd, Srbija; 2016.