The prevalence of C807T mutation of glycoprotein Ia gene among young male survivors of myocardial infarction: a relation with coronary angiography results

Krzysztof Lewandowski[1], Anna Świerczyńska[2], Piotr Kwaśnikowski[2], Waldemar Elikowski[3], Mirosław Rzeźniczak[3]

[1]Department of Haematology, University of Medical Sciences, Poznań, Poland
[2]Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland
[3]Department of Cardiac Surgery, Józef Struś City Hospital, Poznań, Poland

Abstract

Introduction: The glycoprotein complex Ia/IIa (GP Ia/IIa) is a major collagen receptor on platelets and other cell types. Recently, linked polymorphisms within the coding region of the GP Ia gene (C807T and G873A) related to GP Ia/IIa surface expression have been identified. The 807T/873A allele is associated with high expression, whereas the 807C/873G allele is associated with low surface expression of GP Ia/IIa. Subsequently, the 807T allele was found to be associated with coronary artery disease (CAD) and cerebral infarction in younger patients. Moreover, platelet thrombus formation is significantly influenced by genetic variations of the GPIb alpha and GPIa receptors and is dependent on the blood flow rate.

Aim: 1. To determine the frequency of C807T polymorphism of the GPIa gene in young survivors of myocardial infarction (MI) and 2. to evaluate the relationship between the intensity of CAD in the coronary angiography examination and the 807C/T genetic status of the patients.

Methods: 102 young male survivors of MI (YSMI) – mean age 43, range 29-49 years, mean age at the time of the first episode 37±3 years – were studied. Obesity was found in 15%, diabetes in 14%, hyperlipidemia in 87%, hypertension in 22% and smoking history in 90% of cases. Familial CAD and/or MI were confirmed in 50% of patients. The control group consisted of 106 healthy volunteers with a negative family history of CAD, both medical staff members and blood donors (mean age 40, range 18-42 years). The genetic study was performed using genomic DNA obtained from peripheral blood leukocytes. The C807T polymorphism of platelet glycoprotein Ia (GPIa) was investigated using the PCR method introduced by Santoso et al.

Results: Coronary angiography (Siemens Bicor system) revealed single-artery disease in 34%, two-artery disease in 36% and three-artery disease in 26% of patients. In two patients there were no signs of CAD. The C807T polymorphism of GPIa was found in 73.5% of investigated patients (heterozygotes CT 59.8%, homozygotes TT 13.7%). The CC genotype was confirmed in 26.5% of patients. A similar analysis performed in the group of healthy men showed C807T polymorphism of the GPIa gene in 73.6% (CT in 58.5% and TT in 15.1% of persons, ns). CC genotype was found in 26.4% of persons. Interestingly, the T genotype frequency was similar in patients with three- or two-artery disease in comparison with patients with single-vessel or without CAD (49.3% vs. 50.7%, respectively, ns). In 75 YSMI carrying C807T polymorphism of the GPIa gene additional genetic abnormalities were confirmed in 21 patients – BclI polymorphism of β-chain fibrinogen gene, G4070A and G1691A (FV Leiden) mutation of factor V gene and C677T polymorphism of methylenetetrahydrofolate reductase gene. Partial occurrence of combined polymorphisms was found. This was confirmed independently of the number of coronary arteries involved.

Conclusions: Our results may question the potential role of C807T the GPIa anomaly as a single genetic abnormality predisposing young men to coronary artery disease.

Key words: myocardial infarction, C807T polymorphism of the GPIa gene, coronary angiography

Kardiol Pol 2005; 63: 107-113

Address for correspondence:
Dr. Krzysztof Lewandowski, Katedra i Klinika Hematologii i Chorób Rozrostowych Układu Krwiotwórczego, Akademia Medyczna, ul. Szamarzewskiego 89, 60-569 Poznań, Poland, tel.: +48 61 854 93 45, fax: +48 61 854 93 56, e-mail: krzysztof.lewandowski@sk1.am.poznan.pl
Received: 15 July 2004. **Accepted:** 10 June 2005

Introduction

In recent years, several variants of platelet cell membrane glycoproteins (GP) that facilitate thrombotic complications within arterial vessels have been described. These include glycoprotein IIIa PI^{A2} (Leu/Pro) and GPIIb (Ile/Ser) variants. Presence of the GPIIb Ile/Ser isoform has been associated with an increased risk of acute myocardial infarction (AMI) in young women, especially in smoking subjects, with a high serum cholesterol level and a positive family history of coronary heart disease [1]. A similar association has not been found in young men receiving treatment for MI [2].

Other isoforms of different platelet cell membrane GPs reflecting their gene polymorphisms may also play a significant role in arterial thrombosis. One of them is GPIIb/IIIa ($\alpha_{IIb}\beta_3$) fibrinogen receptor point mutation, known as PI^A polymorphism [3]. Two isoforms of PI^A have been identified so far with 1565 codon of the gene for β_3 protein variants 33Leu-PI^{A1} and 33Pro-PI^{A2}. Furthermore, point mutations of genes for alloantigens Br^a/Br^b (HPA–5) and Sit^a (HPA–12bw) as well as genetic defects resulting in altered collagen receptor GPIa/IIa function may also have a significant impact on increased thrombotic risk. Two of them, GPIa gene C807T and G873A mutations, have been most extensively studied. They do not result in an altered amino acid sequence of GPIa but increase platelet GP cell membrane expression. Studies have shown that in subjects carrying the T807C873 mutation GPIa/IIa expression is higher, whereas in carriers of C807G873 it is lower than in persons without the defect [4]. Moshfegh et al were the first to demonstrate in 1999 the association between this genetic polymorphism and MI. An increased risk of AMI in their group however was only found in patients homozygotic for TT defect, regardless of age [5].

Our study aimed to define an association between the GPIa gene C807T polymorphism and prevalence of MI in young men. Additionally, we examined potential associations between atherosclerotic burden assessed during coronary angiography and the presence of different forms of the GPIa gene, as well as other procoagulant states likely to influence the course of coronary heart disease. We were inspired to do so by the reports of others [6] suggesting that homozygotic C877T GPIa gene might be related to resistance to anticoagulant doses of aspirin.

Methods

Patients

A group of 102 young male survivors of MI was studied (aged 29-49 years, mean 43 years, mean age at the time of the first episode 37±3 years). Severity of atherosclerotic coronary heart disease was assessed using coronary angiography (Siemens Bicor). Single-vessel disease was documented in 34% of patients, two-vessel lesions in 36% of patients and three-vessel coronary disease in 26% of patients. In 4 patients no angiographic lesions were found. Obesity (defined as body mass index >30) was recognized in 15% of patients, diabetes mellitus in 14%, hyperlipidemia in 87% and hypertension in 22%. Ninety percent of studied patients smoked cigarettes. A family history of coronary heart disease and MI was documented in 50% of patients. In the previous [4] analysis of prevalence of other potentially prothrombotic haemostatic abnormalities, 4% of studied patients were confirmed to have FV Leiden mutation, 18% had R2 haplotype of factor V gene (FVR2), 3% had G20210A polymorphism of prothrombin gene and 40% had thermounstable variant (nt677C→T) of methylenetetrahydrofolate reductase gene (homozygotic in 5%). In patients after MI 40.7% had β-chain fibrinogen gene Bcl/ polymorphism (βFb) (homozygotic in 3.7%). At the same time, the presence of β-chain fibrinogen gene Bcl/ polymorphism (βFb) was associated with increased fibrinogen blood concentration. In 7% of patients coexisting defects were found (gene βFb Bcl/ polymorphism and MTHFR gene FVR2 or C677T polymorphism as well as prothrombin gene G20210A polymorphism with MTHFR gene C677T mutation [7]).

The **control group** consisted of healthy individuals (n=106) with a negative family history of coronary heart disease, both medical staff members and blood donors (aged 18-42 years, mean 40 years).

Genetic study

Antecubital vein-derived full blood samples were used for genetic studies. Genomic DNA was isolated from pooled peripheral blood leukocytes with *QIAamp DNA Blood Mini Kit* (*Qiagen*). Platelet GPIa C807T polymorphism was assessed using the allele-specific PCR method introduced by Santoso et al [4]. Genomic DNA isolated from peripheral blood leukocytes was used as an amplification matrix (UNO II [Biometera] thermocycler). Reagents contained buffer 3 µl 10x, Taq DNA polymerase 2 µl and deionized water 22 µl. The following PCR protocol was used: initial matrix denaturation – 2 min at 94°C, then 35 repeated cycles, each including matrix denaturation for 30 sec at 94°C, starters binding for 30 sec at 56°C, starters elongation for 30 sec at 72°C, and final starters elongation for 5 min at 72°C with reagents cooling down to 4°C. The PCR protocol was optimised by trial and error, with initial thermal parameters proposed by the Oligo program. To confirm specificity of the ASO-PCR each reaction cycle included a negative control specimen deprived of the studied DNA. A negative result

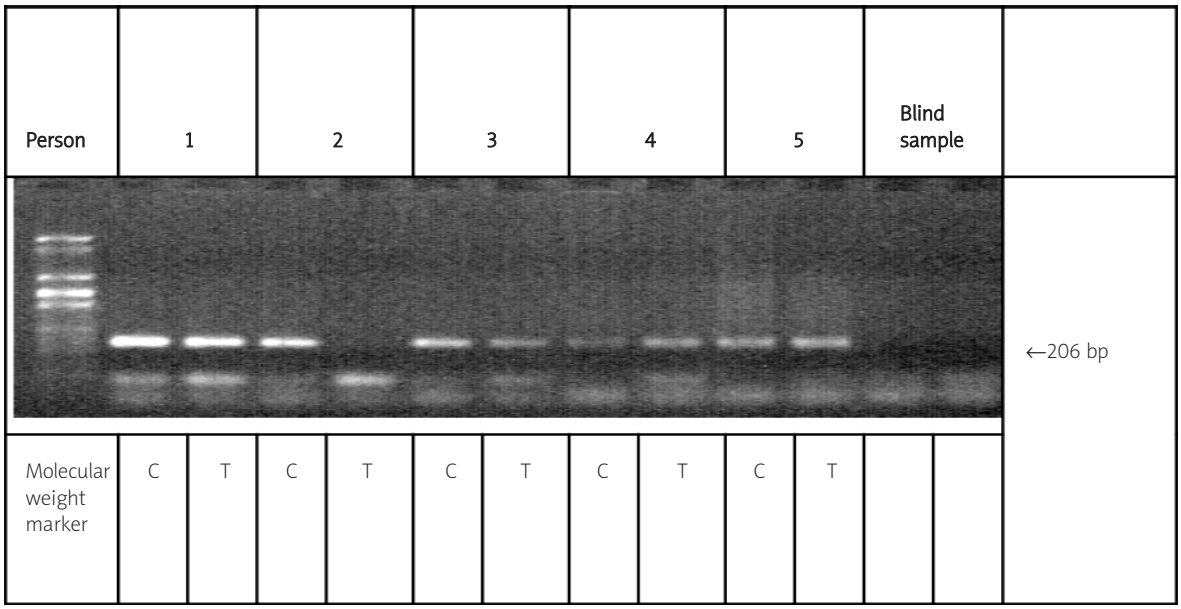

Figure 1. Electrophoresis of products of allele-specific PCR in 1.8% agarose gel. After staining with ethidum bromide visualization using Ultra Violet Product, UVP Gel Analysis SW2000 aparatus was performed. Person 1, 3, 4 and 5 – heterozygotes CT, person 2 – CC homozygote of C807T polymorphism of the GPIa gene

of PCR for negative control was required to continue with PCR analysis. Presence of factor V Leiden, factor V gene G4070A polymorphism, MTHFR gene C677T mutation and β-chain fibrinogen gene Bcl/ polymorphism (βFb) was confirmed using methods presented elsewhere [7, 8].

PCR reaction products underwent 1.8% agarose gel electrophoresis (PCR product 6 µl and load 2 µl of loading buffer). Results of gel electrophoresis were assessed using a dedicated device (Ultra Violet Product, UVP Gel Analysis SW2000). Examples of PCR products analysis and interpretation are shown in Figure 1.

Statistical analysis

Statistical analysis was performed using Statistica for Windows software; a significance level of $p<0.05$ was accepted. Differences of the prevalence of genotypes in studied groups were evaluated with both u-Gauss analysis and the Chi^2 test.

Results

The gene GPIa C807T polymorphism analysis in 102 patients with MI before the age of 40 has shown that genotype CC is present in 26.5%, CT in 59.8% and TT in 13.7% of these patients. A similar analysis in 106 healthy subjects presenting without resting ECG and treadmill test abnormalities has proven similar genotype distribution: CC homozygotic in 26.4%, CT heterozygotic in 58.5% and TT homozygotic in 15.1% of patients.

The prevalence of allele T associated with increased platelet cell membrane expression of the GPIa was similar in healthy subjects and young male survivors of MI (73.5% and 73.6%, respectively, ns).

The prevalence of different genotypes of the GPIa gene C807T polymorphism in relation to the number of coronary arteries affected is shown in Table I.

In patients with GPIa gene C807T polymorphism in many cases also the β-chain fibrinogen gene Bcl/ polymorphism was found, often associated with other procoagulant states. These coexisting abnormalities were observed more often in patients without angiographic coronary lesions or with single-vessel disease (Table II).

In 21 out of 75 young male survivors of MI with GPIa gene C807T polymorphism the following additional genetic changes facilitating thrombosis were documented: β-chain fibrinogen gene Bcl/ polymorphism, factor V gene G4070A and G1691A (factor V Leiden) polymorphisms and C677T mutation of the methylenetetrahydrofolate reductase gene. In some patients multiple abnormalities were found. Their prevalence did not correlate with the number of arteries affected (Table II).

Discussion

Studies investigating the role of procoagulant states in the development of arterial thrombosis have so far been inconclusive. The postulated association between several established venous thrombosis risk factors and

Table I. Relation between the number of coronary arteries involved and platelet glycoprotein Ia 807T gene allelic status in young male patients after myocardial infarction

Number of coronary arteries involved	Homozygotes CC % (n=27)	Carriers of CT and TT alleles % (n=75)	P
0-1	62.9 (17)	49.3 (37)	ns
2-3	37.1 (10)	50.7 (38)	ns

Table II. The occurrence of additional prothrombotic defects in young male patients with myocardial infarction carrying C807T polymorphism of platelet glycoprotein Ia (n=75): a relation with coronary angiography results

Defect	Number of coronary arteries involved		
	0-1	2	3
Bcl/ β-fbg	5	5	–
G4070A FV	1	–	1
C677T MTHFR	2	1	2
F V Leiden	–	1	–
Bcl/ β-fbg + G4070A FV	–	–	1
Bcl/ β-fbg + C677T MTHFR	2	–	–
Total	**10**	**7**	**4**

Abbreviations: BclI β-fbg - BclI polymorphism of β-fibrinogen chain gene, G4070A FV - G4070A polymorphism of factor V gene, C677T MTHFR – C677T polymorphism of methylenetetrahydrofolate reductase gene

extension of coronary heart disease has not been confirmed. This is true for the factor V Leiden which is responsible for factor Va protein C system mediated breakdown resistance as well as for prothrombin gene G20210A polymorphism that leads to increased prothrombin blood levels [9, 10]. Methylenetetrahydrofolate reductase gene C677T mutation (common among persons of Caucasian race) facilitating increased serum homocysteine concentration and thus endothelial injury also does not seem to directly increase the risk of symptomatic coronary heart disease [11, 12].

Inappropriate platelet activation in vivo is probably critical for the development of arterial lesions. Fibrous thrombus formation at the site of vascular injury may significantly reduce blood flow in the affected vessel. This is confirmed by the finding that in subjects with certain genetic variants of the platelet glycoprotein Ia (GPIa) the rate of fibrin thrombus development is increased when high shear stress is applied [13]. The role of platelet cell membrane glycoprotein mutations was confirmed by documentation of an association between certain polymorphisms and excessive reactivity of thrombocytes to physiological procoagulant triggers. As an example, C807T and G873 gene mutations lead to $\alpha_2\beta_1$ integrin dysfunction without GPIa amino acid sequence alteration, but with an evident increase in GPIa/IIa expression in patients with the 807T allele [14]. In high shear stress conditions GPIa mediates initial platelet adhesion to collagen fibres that together with $\alpha_{IIb}\beta_3$ integrin facilitate platelet surface prothrombin conversion and fibrin thrombus formation. An allele form of GPIa seems to play a major role in this process [15]. In their study on GPIa gene polymorphisms, Kunicki et al [14] documented high platelet cell membrane GPIa expression in patients with the 807T allele. The discussed abnormality has been confirmed to play a significant role in the development of MI in patients aged <62 years, with a stronger correlation the younger patients were analysed [4].

Our data show similar prevalence of GPIa gene 807T allele in both young male MI survivors and healthy subjects. Similar findings were presented by Beckerath et al, who reported homozygotic CC in 36.5%, CT in 46.7% and TT in 16.8% of patients [16]. Studies investigating the role of GPIa gene C807T mutation in the course of coronary heart disease in young men have so far been inconclusive. Santoso et al [4] confirmed a positive correlation between C807T mutation and incidence of coronary heart disease in male patients below the age of 49 years. Benze et al [17] failed to demonstrate such a correlation in patients who experienced MI before the age of 45 years. Presence of C807T mutation may facilitate coronary artery occlusion in patients with advanced atherosclerotic lesions. This however was not specifically studied.

Our results do not support the postulated association between atherosclerotic coronary burden and the prevalence of certain allele forms of GPIa gene C807T polymorphism. Partially similar findings were reported by Santoso et al [4], who investigated 2237 male patients in a study that showed a significant correlation between the presence of GPIa gene C807T polymorphism and MI at a young age. However, an association between GPIa gene C807T polymorphism and the development of small atherosclerotic plaques involving

main coronary vessels could not be ruled out. Under certain circumstances the presence of such lesions may lead to abrupt vessel occlusion with platelet thrombus and subsequent MI in patients with GPIa gene C807T polymorphism.

The body of evidence suggests that coronary heart disease predisposition is multifactorial (polygenic). In the review of studies investigating the impact of single genetic polymorphisms on AMI risk Wu et al confirmed a significant risk increase only with $PL^{A1/A2}$ and TT homozygotes of C677T mutation of the MTHFR gene. Neither prothrombin gene G20210A polymorphism nor factor V Leiden significantly affected that risk [9]. Our results support the multifactorial background of MI, documenting additional defects facilitating thrombotic complication in studied patients. Other factors that definitively enhance atherogenesis may also play a major role in acute coronary occlusion [18]. Complex pathogenesis of coronary heart disease is further confirmed by our estimates of β-chain fibrinogen gene Bcl*I* and MTHFR gene C677T polymorphism prevalence in patients with GPIa gene C807T polymorphism as well as by documented coexistence of multiple defects in patients with minimal coronary atherosclerotic lesions.

Relations between certain procoagulatory abnormalities and coronary heart disease incidence, including MI, should perhaps be investigated prospectively and only in young populations. This concept is supported by Hessner et al, who analysed the relationship between prevalence of selected genetic polymorphisms and the age of studied subjects. They found that in patients aged 17-39 years GP $PL^{A1/A2}$ polymorphism was present in 17.5% of patients, but in patients >60 years in only 14.1% of patients. Interestingly, in the same age groups a similar pattern of prevalence of angiotensin converting enzyme insertion/deletion abnormalities (I/D ACE) in patients with DD genotype was observed [19]. These data support the concept of the selective nature of certain genetic abnormalities. It is likely that some of them may facilitate the development of atherosclerotic plaques or thrombosis in coronary arteries, which results in excessive mortality of patients carrying such defects.

Our results as well as reports of other investigators analysing prevalence of single "procoagulant" genetic polymorphisms in patients with established coronary heart disease do not reflect the real risk of thrombotic and atherosclerotic coronary complications. This is especially true for small retrospective studies enrolling patients regardless of their age.

Conclusions

1. Our results do not support the postulated role of C807T GPIa polymorphism in the development of atherosclerotic coronary lesions in young male MI survivors.
2. Common coexisting abnormalities that facilitate thrombosis may support the concept of multifactorial pathogenesis of coronary heart disease.

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Mutacja C807T genu glikoproteiny Ia u młodych mężczyzn po zawale serca. Związek z zaawansowaniem zmian miażdżycowych w tętnicach wieńcowych

Krzysztof Lewandowski[1], Anna Świerczyńska[2], Piotr Kwaśnikowski[2], Waldemar Elikowski[3], Mirosław Rzeźniczak[3]

[1]Katedra i Klinika Hematologii i Chorób Rozrostowych Układu Krwiotwórczego, Akademia Medyczna, Poznań
[2]Instytut Chemii Bioorganicznej, PAN, Poznań
[3]Oddział Kardiochirurgii, Szpital Miejski im. Józefa Strusia, Poznań

Streszczenie

Wprowadzenie: Kompleks glikoprotein Ia/IIa (GP Ia/IIa) jest głównym receptorem dla kolagenu na powierzchni płytek krwi, a także w innych typach komórek. Ostatnio zidentyfikowano polimorfizmy w obrębie genu GP Ia (C807T i G873A) wpływające na ekspresję GP Ia/IIa na powierzchni płytek krwi. W przypadku obecności allelu 807T/873A ekspresja GP Ia/IIa na powierzchni płytek krwi jest wyższa, a w przypadku allelu 807C/873G niższa. Obecność allelu 807T okazała się także predysponować do zawału serca, a także udaru mózgu u młodych osób. Wykazano również, że tworzenie skrzepu płytkowego w określonych warunkach przepływu krwi jest uzależnione od zmian genetycznych warunkujących strukturę receptora GPIbα i GPIa.

Cel: 1. Określenie częstości polimorfizmu C807T GPIa u osób, które przeżyły zawał serca w młodym wieku. 2. Ocena związku pomiędzy rozległością zmian w naczyniach wieńcowych w badaniu koronarograficznym a obecnością allelu C lub T w pozycji 807 genu GPIa. W grupie badanej znalazło się 102 młodych mężczyzn po zawale serca (wiek średnio 43, zakres 29-49 lat, średni wiek w chwili wystąpienia pierwszego epizodu 37±3 lat). U 15% badanych osób wykazano otyłość, u 14% cukrzycę, u 87% hiperlipidemię, u 22% nadciśnienie tętnicze, a u 90% nikotynizm. Rodzinne występowanie choroby wieńcowej i/lub zawału serca potwierdzono u 50% badanych. Grupę kontrolną stanowiło 106 zdrowych osób, z ujemnym wywiadem rodzinnym dotyczącym choroby wieńcowej, rekrutujących się spośród personelu medycznego oraz dawców krwi (w wieku 18–42 lata, średni wiek 40 lat).

Metody: Badania molekularne przeprowadzono na genomowym DNA uzyskanym z leukocytów krwi obwodowej. Polimorfizm C807T płytkowej glikoproteiny Ia oceniono z użyciem PCR metodą wg Santoso i wsp.

Wyniki: Angiografia naczyń wieńcowych (system Siemens-Bicor) uwidoczniła chorobę jednego naczynia u 34%, dwóch naczyń u 36% i trzech naczyń wieńcowych u 26% badanych mężczyzn. U dwóch pacjentów nie wykazano zmian w naczyniach wieńcowych. Polimorfizm C807T genu GPIa wykazano u 73,5% badanych pacjentów (heterozygoty CT 59,8%, homozygoty TT 13,7%). Genotyp CC stwierdzono u 26,5% chorych. Podobna analiza przeprowadzona w grupie kontrolnej osób zdrowych wykazała obecność polimorfizmu C807T GPIa u 73,6% badanych (CT u 58,5% i TT u 15,1%, ns). Genotyp CC wykazano u 26,4% ocenianych osób. Częstość występowania genotypu T była podobna u osób z chorobą dwóch i trzech naczyń w porównaniu z pacjentami bez zmian w naczyniach wieńcowych lub z chorobą jednego naczynia (odpowiednio 49,3% vs 50,7%, ns). U 21 spośród 75 osób po przebytym zawale serca z obecnym polimorfizmem 807T genu GPIa znaleziono dodatkowe anomalie genetyczne – polimorfizm BcI/ genu łańcucha β fibrynogenu, polimorfizm G4070A i G1691A (FV Leiden) genu czynnika V krzepnięcia oraz polimorfizm C677T genu reduktazy metylenotetrahydrofolianowej. Obecność dodatkowych anomalii wykazano niezależnie od ilości zajętych naczyń wieńcowych.

Wnioski: Uzyskane wyniki wydają się nie przemawiać za istotnym znaczeniem wariantu polimorficznego C807T genu GPIa jako izolowanego czynnika predysponującego do choroby wieńcowej u młodych mężczyzn.

Słowa kluczowe: zawał serca, polimorfizm C807T genu GPIa, koronarografia

Kardiol Pol 2005; 63: 107-113

Adres do korespondencji:
dr hab. med. Krzysztof Lewandowski, Katedra i Klinika Hematologii i Chorób Rozrostowych Układu Krwiotwórczego, Akademia Medyczna, ul. Szamarzewskiego 89, 60-569 Poznań, tel.: +48 61 854 93 45, faks: +48 61 854 93 56; e-mail: krzysztof.lewandowski@sk1.am.poznan.pl