Seroprevalence of hepatitis and human immunodeficiency virus in multitransfused patients from a pediatric hematology clinic

Çocuk hematoloji kliniğinde çok sayıda transfüzyon alan hastalarda hepatit ve insan immün yetersizlik virus sıklığı

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Abstract

Objective: Transfusion transmitted hepatitis has been a severe problem in Turkey in pediatric cancer patients and in chronic congenital anemia. The aim of the present study was to investigate the prevalence of hepatitis B, hepatitis C and human immunodeficiency virus infections in these patients in a University Hospital.

Material and Methods: Multi-transfused 66 children (59 acute leukemia, 6 thalassemia major, 1 severe hereditary spherocytosis) diagnosed and followed-up between May, 2000 and December, 2006 were evaluated. Screening of all the patients for HbsAg, anti-HBs, anti-HBc, anti-HCV and anti-HIV was performed at presentation and during the last follow-up. Serologic studies of leukemic patients were also repeated at the end of the chemotherapy. Hepatitis B vaccination was administered to unvaccinated patients with anemia. All blood products were provided by Blood Bank of the Center.

Results: No patient was found HBsAg, anti-HCV or anti-HIV positive at diagnosis and at the end of the therapy. There was history of hepatitis B vaccination in only 42% of the patients at diagnosis due to administration of this vaccine to newborns since 1998. At the beginning of the study, 45 % (n=27) of the leukemic patients were immune for hepatitis B, but after completion of the intensive chemotherapy seropositivity persisted in only 28.8 % (n=17).

Conclusion: Transmission of these viruses is no longer a real problem even in multitransfused immunosuppressed children in Pediatric Hematology Units as a result of the improvements in screening of voluntary blood donors, administration of disposable material in clinics and vaccination by hepatitis B. (*Turk J Hematol 2008; 25: 176-80)*

Key words: Children, chronic anemia, hepatitis, HIV, leukemia.

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Özet

Amaç: Transfüzyon ile bulaşan hastalıklar kanserli ve kronik konjenital anemili çocuklarda ciddi problem oluşturmuştur. Çalışmanın amacı hepatit B, hepatit C ve insan immün yetersizlik virusu sıklığını bir üniversite hastanesinde tedavi gören bu grup hastada belirlemektir.

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Yöntem ve Gereçler: Mayıs 2000-Aralık 2006 döneminde çok sayıda transfüzyon almış 66 çocuk (59 akut lösemi, 6 talasemi major, 1 ağır herediter sferositoz) değerlendirildi. HbsAg, anti-HBs, anti-HBc, anti-HCV and anti-HIV taraması tanı ve son takipte gerçekleştirildi. Lösemili hastalarda kemoterapi bitiminde seroloji tekrarlandı. Anemili hastalar aşılanmamışsa Hepatit B aşısı tanı sırasında yapıldı. Tüm kan ürünleri hastane kan bankasından sağlandı.
Bulgular: Tanı sırasında ve tedavi bitiminde hastaların hiçbirinde HBsAg, anti-HCV veya anti-HIV pozitif değildi. Tanı sırasında hastaların %42 sinde 1998 sonrasında başlayan yenidoğan aşılama programı ile ilişkili olarak hepatit B aşısı öyküsü vardı. Çalışma başlangıcında lösemili hastaların %45 i (n=27) hepatit B için immün idi fakat yoğun kemoterapi tamamlandığında seropozitiflik hastaların sadece %28,8 (n=17) inde devam etti.
Sonuç: Sonuç olarak gönüllü kan vericilerinin serolojik taramalarındaki iyileşme, kliniklerde tek kullanımlık malzemelerin tüketimi ve hepatit B aşılaması sonucu Çocuk Hematoloji Ünitelerinde çok sayıda transfüzyon alan immündeprese hastalarda dahi transfüzyonla bulaş artık önemli bir problem oluşturmamaktadır.
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Anahtar kelimeler: Çocuk, hepatit, HIV, kronik anemi, lösemi

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Introduction

Multiple or life-long transfusions are unavoidable in children with acute leukemia and in patients with chronic congenital anemia. Although survival has increased dramatically in parallel to advances in chemotherapy and chelation, transfusion-transmitted hepatitis has been a severe problem in Turkey, especially in pediatric cancer patients [1-3]. HBsAg positivity was even as high as 40% in pediatric cancer patients diagnosed between 1986 and 1989 [1]. A study from Japan from nearly the same period reported that in childhood acute lymphoblastic leukemia (ALL) survivors diagnosed between 1984 and 1990, hepatitis C infection rate was 9% [4]. Reduction in the transmission of these viruses depends on the decrease in infection prevalence in the population by improvement in life standards and effective education about transmission routes, better screening of voluntary blood donors, administration of disposable material in the hospitals, and vaccination of the population for hepatitis B.

In a large multi-center study covering 22 Red Crescent Blood Banks throughout the country, it was reported that seroprevalence of hepatitis B and hepatitis C decreased markedly between 1989 and 2004 in Turkey [5].

In this study, we aimed to investigate hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections in multi-transfused patients diagnosed and followed between 2000 and 2007 in a pediatric hematology unit of a university hospital.

Materials and Methods

Approval of the Hospital Ethics Committee and informed consent of parents were obtained for the study. Pediatric patients with acute leukemia and chronic anemia, diagnosed and followed since foundation of the Center in May 2000 until the end of December 2006 were evaluated. Hospital records of all patients with acute leukemia and chronic congenital anemia were investigated for history of vaccination, hepatitis and HIV serology. Patients with leukemia who had a short follow-up due to early death with complications other than hepatitis or HIV infection were excluded. Screening for HbsAg, anti-HBs, anti-HBc, anti-HCV and anti-HIV was performed with a qualitative third-generation microparticle enzyme immunoassay (Abbott Axsym System® assay). During follow-up serology, transaminases and if necessary HBV-DNA or HCV-RNA studies were performed. Patients with thalassemia major and hereditary spherocytosis were vaccinated at diagnosis with hepatitis B vaccine (3 injections at a dose of 10 µg) if they were seronegative. Vaccination of seronegative leukemic patients was planned following the third month of maintenance therapy. All blood products were supplied by the blood bank of the hospital from unpaid donors. Generally directed donors provided by the families and rarely voluntary donors were the source of blood supply. In chronic anemia, some families could provide most antigenic subgroup antigens also matched (Rh and Kell antigens) repeated donors for prevention of alloimmunization and reducing the number of donor exposures. Number of transfusions and exposure time to transfusions (from beginning of the first transfusion to the last transfusion) were also recorded. Pretransfusion levels were: hemoglobin <8.5 g/dl and platelet count <20,000/mm^3 in leukemia and hemoglobin 9-9.5 g/dl for patients with thalassemia.

Serological screening was repeated before vaccination in leukemic patients and during the last visit of patients with thalassemia major and hereditary spherocytosis.

Inactive carrier state was defined as normal alanine aminotransferase (ALT) level, positive HBsAg, negative HBeAg and less than 100,000 copies/ml HBV-DNA. Chronic infection was described as persistence of HBsAg in serum for at least six months with evidence of active viral replication (HBeAg and/or HBV-DNA). Polymerase chain reaction (PCR) testing for HCV-RNA was studied when anti-HCV was positive or when ALT levels were elevated to show active infection. Persistence of HCV-RNA beyond six months identified chronic hepatitis C infection [6].

Descriptive statistics were performed by SPSS version 13.

Results

Fifty-nine patients with acute leukemia (47 ALL, 12 acute myeloblastic leukemia), 6 with thalassemia major and 1 with severe hereditary spherocytosis were enrolled in the study.

There were 35 boys and 31 girls, with a median age of 6.1± 4.2 years (2 months-16.7 years) at diagnosis. The mean ages of the leukemic patients and patients with anemia were 5.25 years (2 months-16.7 years) and 0.6 years (40 days-16 months) at diagnosis, respectively.

There were no hepatitis B or hepatitis C carriers or HIV-positive patients at diagnosis. A modified BFM 95-ALL chemotherapy protocol and AML-MRC 10 protocol were administered. Fifty-nine percent (n=35) of leukemic patients had no hepatitis B vaccination before diagnosis. Thirty of these patients were born before 1998, when the hepatitis B vaccination was not included in the national vaccination schedule. However, 6 unvaccinated children were anti-HBs- and anti-HBc IgG-positive at diagnosis. There were 3 anti-HBs- negative patients among vaccinated leukemic patients. During chemotherapy, no acute viral hepatitis or carrier was detected. At the end of the intensive chemotherapy, 6 of the vaccinated leukemic children lost immune response. At the beginning of the study, 45% (n=27) of the leukemic patients were immune but after completion of intensive chemotherapy, seropositivity persisted in only 28.8% (n=17) of the patients (Figure 1).

Only 4 of the 7 anemic patients were vaccinated and anti-HBs-positive at diagnosis; for the remaining 3 patients, vaccination was started at diagnosis and all had anti-HBs positivity during follow-up.

There was no anti-HCV or anti-HIV seropositivity during follow-up of the enrolled patients. Exposure time for transfusions was a median 0.6 (0.02-4.39) patient years for the whole group; 0.6 (0.02-3.35) patient years for leukemia and 2.7 (0.29-4.39) patient years for chronic anemia. Six of the patients with leukemia were also followed during relapse; others were followed at least until the beginning of maintenance. During chemotherapy, the median number of transfusions for patients with leukemia was 13 (6 apheresis units of platelet, 7 units of packed red cell), while the median number of transfusions was 32 units of packed red cells for those with chronic anemia (Table 1).

Discussion

Patients with acute leukemia are immunosuppressed by nature of the disease and as a major side effect of the antineoplastic drugs. A recent study showed that immune reconstitution of T-cell, B-cell and NK cell subsets is not gained for at least six months following therapy, and reconstitution is even more delayed in high-risk groups who receive more intensive chemotherapy [7]. This immunosuppressed state increases risk of blood-borne viral infections.

In Turkey, high HCV prevalence was found in children with thalassemia and cancer (14% and 4.5%) [8]. HBsAg and HCV seropositivity were 0% and 2% at diagnosis and increased to

Table 1.Number of transfusions

	Leukemia (n=59)		Anemia (n=7)	
	Total	Median	Total	Median
Packed red cells (Units)	481	7	223	32
Apheresis platelets (Units)	471	6	-	-
Total	952	13	223	32

n: number

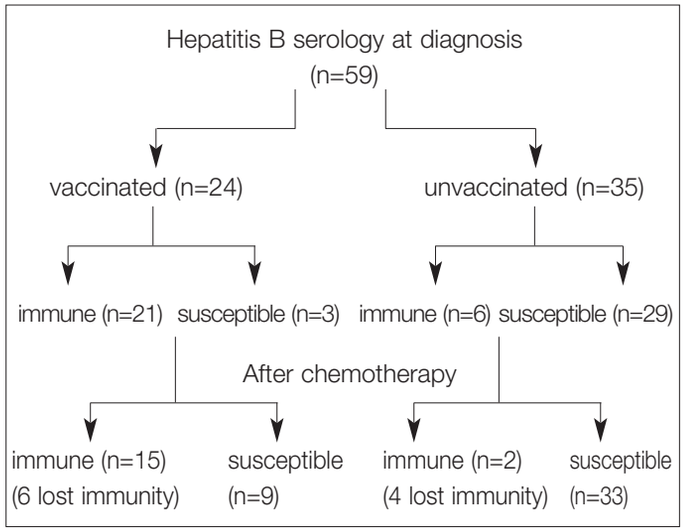

Figure 1. Hepatitis B immunity of patients with acute leukemia

10% and 14%, respectively, at the end of the therapy in children with malignancy diagnosed between 1994 and 1995, but HIV seropositivity remained 0% at diagnosis and following therapy, respectively [2]. Another study from our country enrolling children diagnosed between 1993 and 1998 showed that 14% of children with acute leukemia, 7.5% of solid tumors, and 14.2% with lymphoma were HBsAg-positive at the end of the therapy. In the same study, 5.5% of these 198 patients were HCV-seropositive at the end of the therapy. About half of the HBV-infected patients were infected during chemotherapy. More than half of the HBV- or HCV-infected children developed chronic hepatitis. Thirty-eight of 198 patients were infected and 22 developed chronic hepatitis [3]. In all the studies from our country, hepatitis C prevalence was lower than hepatitis B prevalence.

In a study from the south of the country enrolling 399 multitransfused anemic patients followed since 1996 (beta-thalassemia major, thalassemia intermedia and sickle cell anemia), 3 were HBsAg-positive (0.75%), 18 were anti-HCV-positive (4.5%), and none was anti-HIV-positive. All patients with positive HBsAg and 14 patients with HCV received initial blood transfusions before second-generation tests were performed in local blood banks [9].

It was shown in a national survey of blood bank donors that there has been a gradual decrease in the prevalence of HBsAg, from 5.23% in 1991 to 2.1% in 2004. Seroprevalence of HCV antibody also decreased, from 0.56% in 1998 to 0.34% in 2004 [5]. Our blood bank screening of 9240 blood donors in 2006 showed that 1.1% were HBsAg-positive, 0.27% anti-HCV positive and no donor was anti-HIV- or rapid plasma reagin test-positive (unpublished data from hospital records). There has been an improvement in the blood banks of Turkey. Paid donation was prohibited and the more reliable and sensitive test method of ELISA was introduced in 1983 for screening of HBsAg. In the same year, screening for Treponema pallidum was also introduced. In 1987, anti-HIV was also added to the screening. In 1996, routine screening of HCV by ELISA was also started in addition to routine utilization

of the donor questionnaire forms. Although the number of patients with acquired immunodeficiency syndrome is gradually increasing in Turkey, there were 1601 patients in 2003 according to the records of the Ministry of Health (population of the country in 2003 was more than 70 million) [10].

Hepatitis B vaccination was started in Turkey in 1998, targeting only the newborns. In 2005, vaccination of adolescents was also integrated into the national vaccination schedule. About 42% of our patients were vaccinated before diagnosis.

In a recent report from a pediatric oncology center of our country, it was reported that in patients with lymphoma and solid tumors (n: 95) diagnosed between January 2005 and December 2006, only one patient was HBsAg-positive at diagnosis and all patients were seronegative for HCV. Seronegative patients were vaccinated during chemotherapy, and at the end of the therapy, only one patient was anti-HCV-positive. At diagnosis, 61% of the patients were anti-HBs-positive [11]. Similar to the results of our study, infections with these viruses are no longer a real problem, at least in some of the pediatric oncology centers of Turkey.

In the present study, active immunization of acute leukemic patients was planned during maintenance because studies show that during intensive chemotherapy, vaccine response is very low. It is reported that in children with ALL who complete whole vaccination during intensive chemotherapy, failure is 93% [12]. In a study from our country, seroconversion rate was only 35.1% in children with ALL who were vaccinated during therapy [13]. Revaccination of the children after completion of intensive chemotherapy is recommended [14].

Parallel to our findings, it is reported that chemotherapy protocols in ALL may induce loss of immunity to viral vaccination antigens in some patients [15]. In the present study, 6 of the 24 vaccinated leukemic children lost immune response at the end of the therapy, similar to some naturally immune children. Nevertheless, completion of hepatitis B vaccination before diagnosis remains the most effective prophylaxis. It was shown in an Italian study that at a median 10 months after the end of therapy, humoral immunity against hepatitis B is preserved in 81% of children, which is comparable to healthy children of the same age and same geographical area [16]. In a study from Poland where vaccination for hepatitis B for infants was started in 1995, it was shown that in children with cancer who completed the hepatitis B vaccination course completely or partially before diagnosis, 25% were infected during chemotherapy. Although anti-HBs level was decreased, 79.2% of the infected patients eliminated the virus [17].

Prevalence of hepatitis B infection is still high in some countries. In a study from India, in children with ALL who received active immunization combined with specific hepatitis B immunoglobulin during intensive chemotherapy, infection rate was 17%, and in the group who received active immunization combined with interferon, the infection rate was 59%. The authors stated that interferon failed to serve as a vaccine adjuvant, but in the whole group, the rate of infection had reduced to 27%, which still seems very high [18]. In a study from Venezuela, HBsAg seropositivity was 25% in children with cancer [19].

Passive prophylaxis of hepatitis B by monthly injection of hyperimmunoglobulin during intensive chemotherapy of leukemia was also used in 48 HBV-negative children from our country, and none of them was infected during this period [20]. Passive prophylaxis may be beneficial in these seronegative children, but may not be necessary if blood products are safe. A study from Poland showed that 23.6% of 55 seronegative children with leukemia were infected during chemotherapy despite regular passive prophylaxis [12]. Therefore, it is also possible to say that if blood products and invasive procedures are not safe, passive prophylaxis can not maintain good protection from hepatitis B infection.

Hemovigilance and transfusion-transmitted disease surveillance systems have not been implemented into the transfusion practice of our country. Although our study group and their exposure period is relatively small with regard to the blood component supply of our Blood Bank, this patient cohort has the opportunity of routine follow-up and they reflect in a way transfusion safety for these virus infections. Our pediatric hematology center was founded in 2000 and it is satisfying that blood products and invasive medical procedures are very safe and that no multi-transfused patient, even with immunosuppression, was infected with HBV, HCV or HIV, similar to the developed countries of Europe. Within the Late Effects Surveillance System, 264 relapse-free pediatric sarcoma patients from Germany, Austria and Switzerland treated between 1998 and 2004 were investigated for risk of HBV, HCV or HIV. None of the patients was reported to have acquired HBV, HCV or HIV during antineoplastic therapy [21].

As a result of improvements in blood banks, administration of disposable material in clinics and vaccination for hepatitis B, transmission of hepatitis B, hepatitis C and HIV may no longer be a real problem even in pediatric malignancies.

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