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The Hct values after liver transplantation

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Abstract

In the present study our aims are to evaluate the trend of the Hct values after liver transplantation and the prevalence of post-transplant erythrocytosis, as well as to detect, through a sub-analysis, if the switch to hepatitis B immune globulin therapy SC affects the Hct levels. We retrospectively analysed patients who had undergone liver transplantation and were still followed up at the Liver Following Transplantation Centre of the University of Salerno in December 2016. Our first analysis included 113 subjects. Among them, we identified eight patients with at least one manifestation of high Hct in the last year who needed phlebotomy with a prevalence of post-transplant erythrocytosis at 7.07% (8/113).

All patients were male and had a HBV history, except one with a history of bile ducts atresia. We observed a progressive increase of Hct over time after OLT in all patients. In 2010, 13 HBV patients underwent the switch from hepatitis B immune globulin therapy EV/IM to hepatitis B immune globulin therapy SC, yet the change of formulation did not reduce the Hct values. Our findings show that Hct values increase over time in patients with liver transplantation, but they become pathological only in male patients with HBV infection.

Introduction

Haematocrit (Hct) reflects the whole blood viscosity and its elevation due to erythrocytosis can cause thromboembolic events. Absolute erythrocytosis is defined as a red cell mass (RCM) above 125% of prediction. This can be assumed if the Hctis above 0.60 in a male and 0.56 in a female. It is suspected with an Hct above 0.51 in a male or 0.48 in a female [1]. Causes of absolute erythrocytosis can be primary when there is an intrinsic problem in the bone marrow, and secondary when there is an event outside the bone marrow leading to erythropoiesis. The latter can be divided into congenital and acquired erythropoiesis [1]. Acquired erythrocytosis has been largely described in subjects after kidney transplantation. Post-transplant erythrocytosis (PTE) has been in fact defined as a persistently elevated Hct to a level higher than 51% after renal transplantation. It seems to occur in 10% to 15% of graft recipients and it usually appears 8 to 24 months after engraftment [2-6]. Predisposing factors include male gender, retention of native kidneys, cyclosporine use and a rejection-free course with a well-functioning renal [3]. Patients may require treatment with phlebotomy or angiotensin-converting enzyme inhibitors [4,5]. Acquired erythrocytosis was also described in subjects with simultaneous kidney-pancreas transplant [7] and those with allogeneic hematopoietic stem cell transplantation [8,9]. Based on our knowledge, our group was the first and only to report in 2013 [10] post-transplant erythrocytosis in subjects with liver transplantation. We found that erythrocytosis appeared in 11 males with HBV among 96 adult patients who had undergone OLT for different causes. Therefore, we concluded that a history of HBV infection, male genderand hepatitis B immune globulin therapy were all possible cofactors for an increased risk of erythrocytosis in OLT patients [10]. We designed this new retrospective analysis to evaluate the trend of Hct values after liver transplantation and the prevalence of post-transplant erythrocytosis, as well as to detect, through a sub-analysis, if the switch to hepatitis B immune globulin therapy SC affected the Hct levels.

Methods

We retrospectively analysed patients who had undergone liver transplantation and were still followed up at the Liver Following Transplantation Centre of the University of Salerno in December 2016. Data were collected on age, sex, year, aetiology of liver transplantation, and laboratory indexes. Our patients routinely undergo a haematological evaluation at least twice a year, and all results are archived in a dedicated database.

Firstly, we identified patients with at least one pathological Hct value in the last year and who neededphlebotomy, to analyse the prevalence of post-transplant erythrocytosis in our population. Post-transplant erythrocytosis was defined as an Hct increase >51% in males and as an Hct increase >48% in females. Secondly, we selected only patients whose haematocrit (Hct) records were available in our dataset at 6 months, 12 months, 18 months, 36 months and 48 months after transplantation to analyse the trend of the Hct values after OLT. Thirdly, performing a sub-analysis including only patients with a history of HBV based on our previous results [10], we checked the effect of the switch from hepatitis B immune globulin therapy IV/IM to that SC on the Hct values. This switch was performed in our center in 2010 in patients who agreed to change their current therapy. All subjects gave their informed consent for the study; all procedures were in accordance with the Helsinki Declaration of 1975. The exclusion criteria were a follow-up shorter than two years at our centre, a history of pre-transplant erythrocytosis, kidney or respiratory failure, and a diagnosis of a malignant or non-

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malignant tumour post-OLT. All patients with increased Hct values underwent a focused examination at the haematology department to establish the form: primary, secondary or idiopathic.

Categorical and continuous variables were expressed as frequency and mean (Standard Deviation and range), respectively. Differences in frequencies were calculated using $\chi 2$ test; differences in means were calculated using paired t-test.

Results

Prevalence of Post-transplant erythrocytosis in OLT

In December 2016 our database included 129 patients who had undergone OLT for different causes and were still followed up at our Liver Following Transplantation Centre. Two patients were excluded because of a history of alcohol abuse, four because were followed at our centre for less than two years, five because of recurrent hepatocellular carcinoma after OLT, four because already had a pre-OLT evidence of elevated Hct and one because of a known genetic mutation p.V617F in the Janus kinase 2 gene.

Therefore, we included in our first analysis 113 subjects [mean age in 2016: 62.9 years (SD 10.6); 75 males (66.4%)]. The cause of transplantation was cirrhosis due to HBV in 40 cases, to HCV in 55 cases and other causes of cirrhosis in 18 cases.

Among them, we identified eight patients with at least one manifestation of high Hct in the last year who needed phlebotomy (Table 1) with a prevalence of post-transplant erythrocytosis of 7.07% (8/113). As Table 1 shows, all patients were males and had a HBV history except one with a history of bile ducts atresia. This latter patient had undergone OLT in 1999, but needed a phlebotomy for the first time in 2014.Six HBV patients took hepatitis B immune globulin therapy SC and two EV in 2016.

The Hct trend after OLT

The Hct values were available at 6 months, 12 months, 18 months, 36 months and 48 months after transplantation in 64 patients in the study (65.6% males). The mean age at the liver transplantation was 53.2 years (SD 9.3, range 21-67), the cause of transplantation was cirrhosis due to HBV in 21 cases, to HCV in 32 cases and other causes of cirrhosis in 11 cases. We observed a progressive increase of Hct over time after OLT (Figure 1) in all patients. Five of the seven HBV patients with post-transplant erythrocytosis in 2016 were followed up at our centre from OLT, so the first evidence of erythrocytosis was available in our database (Table 1). As we can see in Table 1, the erythrocytosis raised for the first time within one year from OLT in two patients, and after almost three, four and five years respectively in the other three patients. All patients with HBV history took hepatitis B immune globulin therapy EV at the time of the first evidence of erythrocytosis.

Looking at the Hct over time available for all HBV with post-transplant erythrocytosis from the OLT date or from the follow-up start date in our database, we observed that the Hct values are not constantly high and the necessity of phlebotomy is only occasional over time (*data not shown*).

The role of the hepatitis B immune globulin therapy

In 2010, thirteen of our HBV patients underwent the switch from hepatitis B immune globulin therapy EV/IM to hepatitis B immune globulin therapy SC (including five patients with post-transplant erythrocytosis diagnosis in 2016).

Figure 2 shows in detail the mean values (SD) of Hct in the periods before and after the switch. Comparing the mean values of Hct at 24 months, 12 months and at the time of the switch to those after the switch, the change of formulation did not reduce the Hct values in these patients.

Discussion and conclusion

Our study describes a prevalence of post-transplant erythrocytosis of around 7% in OLT patients. The Hct values increase over time after OLT in all patients, becoming pathological in some HBV males in a non-established time after OLT. In patients with a diagnosis of post-transplant erythrocytosis, the Hct values are not constantly high over time, and the necessity of phlebotomy is occasional. The HBV Ig therapy formulation does not affect the Hct values.

Most of the available literature on the post-transplant erythrocytosis concerns subjects after kidney transplantation in whom it seems to occur in 10% to 15% of cases and usually develops 8 to 24 months after engraftment [2-6]. Comparing to the studies on the kidney transplantation, we described a lower prevalence and an unestablished onset time of post-transplant erythrocytosis (from few months to five years) in OLT patients, but similarly, we found the male gender as a predisposing factor. Even if the population included in the study is not perfectly the same as the previous one [10] (from this time we included only patients still followed up at our center in 2016), we confirm the role of the HBV history and the male gender on the erythrocytosis onset, showing this time the irrelevant role of the HBV Ig therapy. The possible cause of the higher values of Hct remains still unclear post OLT. However, the role of the HBV and the male gender seems sure. HBV infection frequently results in the suppression of haematopoiesis [11]; however, erythrocytosis developed only after OLT and not when HBV was active, and since we showed the irrelevance of the HBV Ig formulation, other possible causes need to be found.

The evidence of erythrocytosis in a patient with a history of bile ducts atresia is probably independent of the post-transplant erythrocytosis and due to other unknown causes.

Table 1. Patients with a Post-transplant erythrocytosis diagnosis in 2016. *Bile ducts Atresia.

Code	Sex	Date OLT	Cause OLT	First Erythrocytosis Evidence	Age (years) Dec 2016	HBV Ig SC in 2016	Immunosuppression therapy	Phlebotomy needed/ 2016
8	M	13/12/96	HBV	13/05/05	59	Yes	MMF	Two
14	M	28/04/01	HBV	12/03/04	47.5	Yes	FK506	Three
16	M	23/02/99	HBV	11/05/99	68	Yes	Ciclosporine	Two
34	M	09/08/00	HBV	19/03/04	58.4	Yes	FK506	One
40	M	16/01/99	HBV	14/07/99	75.4	Yes	Ciclosporine	One
41	M	28/03/97	HBV	Unknown	50.8	No	MMF	Two
79	M	13/01/03	HBV	Unknown	70	No	FK506	One
22	M	23/05/99	Other*	10/06/14	38	-	Ciclosporine	Two

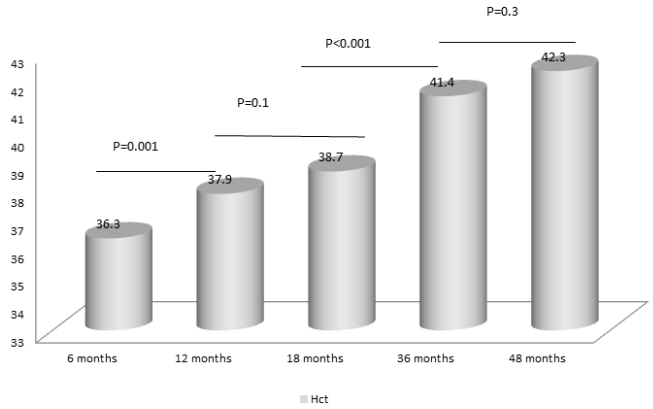
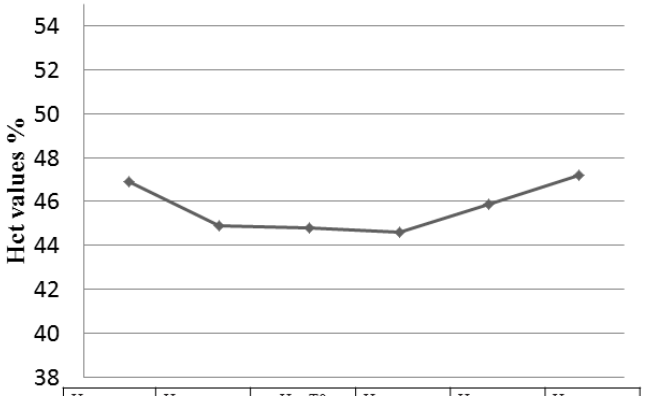


Figure 1. Hct levels over time (6 months, 12 months, 18 months, 36 months and 48 months after OLT).



Hct pre 24 months	Hct pre 12 months	Hct T0 (2010) Switch time	Hct post 12 months	Hct post 24 months	Hct post 36 months
46.9 (4.0)	44.9 (4.3)	44.8 (3.5)	44.6 (4.0)	45.9 (3.9)	47.2 (4.3)

Figure 2. Hct values in HBV patients who switched to anti-HBV SC (13 patients: 11 males).

In this study, we looked for a new and little-known disease in a population from the same region (Campania, Italy), followed at the same centre and undergoinghaematological analysis at the same laboratory, in order to eliminate or reduce any possible external influence on our results. All patients with pathological Hct values underwent a focused examination at the haematology department to confirm the secondary form of erythrocytosis and to establish the correct necessity of phlebotomy. Unfortunately, only in 64 out of 113 patients the Hct values were available from the OLT time; however, we believe it is enough to describe a wide range of onset time (from few months to several years).

In conclusion, our findings describe that Hct values increase over time in patients undergoing liver transplantation, but they become pathological only in male patients with an HBV infection. The cause of this is still unclear, but we showed that the HBV Ig therapy formulation is irrelevant on its onset.

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