

ORIGINAL ARTICLE

A survey on patient perception of reduced-intensity transplantation in adults with sickle cell disease

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The development of reduced-intensity conditioning (RIC) and the success of BMT for paediatric sickle cell disease (SCD) have raised the possibility of revisiting this prospect in adults as well. In a chronic debilitating disorder managed with supportive therapy, the patients' perception is critical in the advancement of any potential curative therapy. To explore this aspect, we undertook a questionnaire-based survey on 30 adults with SCD. Sixty two per cent of the patients were ready to accept a transplant-related mortality (TRM) >10%; 30% of them a TRM >30%. A risk of graft failure (GF) >10% was acceptable to 64%, with a risk >30% acceptable to 41%. Infertility was acceptable to only 50%. Chronic graft-versus-host disease (GVHD) was unacceptable to the majority (80%). Seventy six per cent of patients had a full sibling and 60% were willing to participate in a clinical trial of RIC transplantation. This survey suggests that the majority of adults with SCD might be willing to consider a curative option such as RIC transplantation even with a high TRM or GF. The major concerns relate to chronic GVHD and infertility. There is an urgent need to explore RIC transplants in SCD patients within the framework of a clinical trial, considering patient perception regarding cure and complications.

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Introduction

Significant improvement in the supportive care of sickle cell disease (SCD) in children has resulted in about 85% of these patients surviving beyond the second decade.¹ However, a similar study on survival of those with SCD over the age of 20 years showed a 25–30 years decrease in

life expectancy compared with the general black population, 33% succumbing to sickle-related crisis and another 18% to overt organ failure.²

On the other hand, a review of the studies reporting conventional allogeneic bone marrow transplantation (allo-BMT) in nearly 200 children and adolescents reveal that over 80% of these patients achieve a phenotypic cure with a mortality rate not exceeding 10%.^{3–5} This is, indeed, an impressive outcome, considering the fact that only the most severely affected patients have undergone allo-BMT. Improved survival in children with SCD with energetic supportive management has resulted in a growing adult population with SCD, who have continued, progressive or new problems related to this genetic disease. The encouraging results of allo-BMT in children with SCD have prompted some centres to explore this procedure in young adults. However, this enthusiasm has been short-lasting owing to poor outcome with conventional allografting.⁶

Recent developments in reduced-intensity conditioning (RIC) have rendered allogeneic haematopoietic stem cell transplantation (allo-HSCT) feasible in a wider group of patients who could potentially benefit from such a procedure, but who were considered ineligible for conventional conditioning owing to increased age or comorbidities.^{7–10} Various RIC regimens have been employed with differing complications. Although stable mixed chimerism was thought to be an inevitable outcome following such transplantation, this did not hold good for most RIC regimens. However, some combinations employing *in-vivo* T-cell depletion of the graft have resulted in stable mixed chimerism in a proportion of patients.^{7,11} In a multicenter study from the US and another from Belgium, stable mixed chimerism of between 11 and 74% was documented in several patients associated with phenotypic cure of SCD.^{4,12} Although these studies were not designed to induce mixed chimerism, which was more of a chance occurrence, they do highlight an important aspect of allo-HSCT in SCD, that stable, mixed chimerism might be enough to induce phenotypic cure of SCD.

Based on these considerations, we have recently reviewed the feasibility of developing a RIC-based allo-SCT in adults with SCD.³ Although the possibilities are promising, there are several issues that need to be addressed. Most important is the acceptability of such an intervention to patients with this condition. In a chronic condition with

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high morbidity such as SCD where supportive therapy is available, development of any curative procedure such as allo-HSCT will be influenced by the perception and attitude of the affected patients. In an attempt to explore this issue, we carried out a questionnaire-based pilot survey on 30 adult patients with SCD.

Materials and methods

The study was designed to survey regular attendees at the Regional Haemoglobinopathy Centre, City Hospital, Birmingham as a pilot project. Ethical approval was obtained from the local ethics committee and informed consents were obtained from all participants. The patients were initially briefed about the survey by one of the authors, and were provided with study information. This information consisted of a brief background summary and described the purpose of the questionnaire. They were provided with further detailed information regarding allo-HSCT and its complications, allo-HSCT in SCD and current status of RIC. The information leaflet clearly mentioned that the possibility of RIC transplantation for adults with SCD does not exist in the UK at the current time and is at an experimental stage in other countries. It was also reiterated that the questionnaires would be anonymized after completion and the participant would be under no pressure to participate in any future clinical trials based on the current opinion expressed. Any doubt or query was addressed by one of the authors.

The only demographic data obtained related to the patient's age, gender and type of haemoglobinopathy. The questionnaire consisted of two parts with a total of 18 questions. In the first part, the following questions were asked, (a) quality of life (QOL); (b) number of hospital admissions in the last 2 years; (c) Current employment status; (d) Whether the disease has affected employment opportunities; (e) Had hydroxyurea (HU) (hydroxycarbamide) been offered and if it had been accepted; (f) whether benefit from HU had been derived.

In addition in the first part of the questionnaire they were also asked the following:

(g) Were they previously aware of SCT/BMT before reading the patient information related to this survey; (h) Had this procedure (BMT) been discussed with them at any stage (i) Did they perceive BMT as a curative treatment.

The second part of the questionnaire explored their attitude towards various outcomes related to allo-HSCT. Two issues, namely the acceptance of mortality associated with the procedure (transplant related mortality (TRM)) and the acceptance of failure of this procedure (graft-failure (GF)) without mortality, that is autologous recovery with a return to previous disease state, were explored in a gamble-paradigm as in two previous studies.^{13,14} This was done as follows. In the first situation, allo-BMT/SCT was described as offering 100% cure of SCD without any mortality or GF. In separate questions, the risks of each of these were increased by 5%. In this way, each participant indicated the highest risk of TRM or GF they would accept in lieu of a cure of their condition.

Other aspects explored were as follows: (a) acceptance of infertility in exchange of cure; (b) Acceptance of chronic graft-versus-host disease (GVHD) in exchange of cure; (c) Acceptance of life-long prophylaxis such as penicillin (poor compliance with this drug is an acknowledged problem in adult patients); (d) Availability of a full sibling in the family not affected by SCD; (e) Participation in a future clinical trial on RIC allo-SCT in adults with SCD.

Statistical considerations

The outcome variables in part 2 of the questionnaire were analysed against the demographic data and the data obtained from part 1 of the questionnaire. The binary outcomes were analysed by Fisher's exact test and the continuous variables were analysed using Student's *t*-test.

Results

Thirty patients suffering from SCD (HbSS or HbSC) participated in this survey. The median age of the cohort was 29.5 years (range 18–56 years), 20 women and 10 men. twenty-eight patients had homozygous SCD (HbSS) and two were double heterozygous for HbS and HbC.

Twenty-nine (96%) patients felt that their QOL had been significantly affected. Twenty (66%) were unemployed and 26 (86%) perceived that their employment opportunities were affected by the disease. HU was offered to 17 participants (56%) and 15 of them (88%) accepted the treatment. Only seven patients (46%) felt that they derived any benefit from HU, four were unsure (26%).

Twenty-eight participants (93%) mentioned that they were aware of BMT before reading the patient information leaflet. In only five participants (16%) this had ever been discussed with them or their family. Twenty-six participants (86%) perceived allo-BMT/SCT as a curative option for SCD and one participant was unsure.

The acceptance of various levels of TRM in lieu of a cure for SCD according to the gamble paradigm has been detailed in Figure 1. In brief, if the TRM increased above 10% the procedure would be unacceptable to over a third of the cohort (11 patients, 37.9%). However, a TRM of over 30% was still acceptable to 31% whereas another 31%, of patients found a mortality risk between 10 and 30% acceptable.

The acceptance of GF without mortality is detailed in Figure 2. GF of over 10% was not acceptable to a similar proportion of patients (10 patients, 34.5%). Twelve patients (41.4%) were ready to accept a GF rate of over 30% and for seven patients (24.1%) this was between 10 and 30%.

One participant did not answer either of these questions. The acceptance of various levels of TRM and GF was not influenced by age, gender, employment status, HU treatment and number of hospital admissions. There was no significant association between the levels of acceptance of TRM and GF.

Life-long prophylaxis in lieu of a cure was acceptable to 29 patients (96%). A majority (24 patients, 80%) refused to accept significant chronic GVHD in lieu of a cure of SCD.

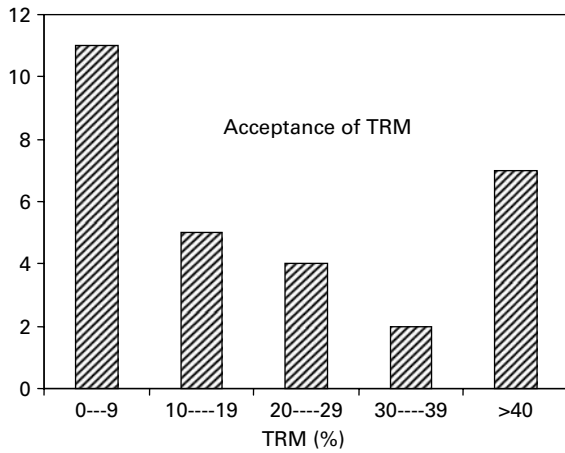


Figure 1 Chart showing the number of patients with SCD who said that a RIC-SCT providing curative option would be acceptable to them at different estimates of TRM. The numbers of patients are shown in the Y-axis and the different ranges of TRM are shown in the X-axis.

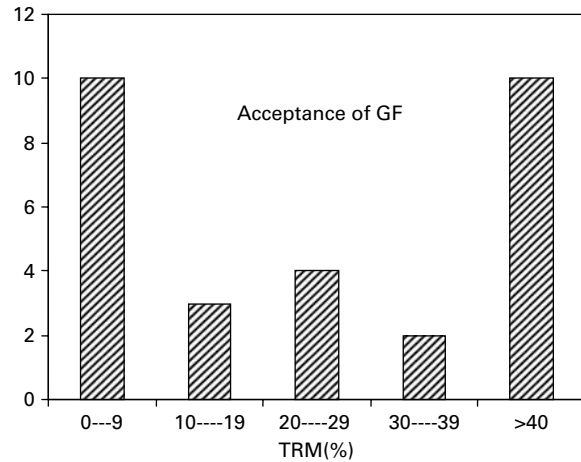


Figure 2 Chart showing the number of patients with SCD who said that a RIC-SCT providing curative option would be acceptable to them at different estimates of GF without mortality (i.e. an autologous recovery). The numbers of patients are shown in the Y-axis and the different ranges of TRM are shown in the X-axis.

Two patients were unsure of it. Infertility was also acceptable to only 15 participants, with two more being unsure about this issue. There was a trend of this complication being less acceptable to male (3/8) than female (12/20), ($P=0.05$). None of these outcomes were affected by other variables.

Finally, 23 (76%) participants had a full sibling unaffected by SCD and 18 participants (60%), given that the TRM and GF were within their acceptance parameters, were agreeable to participate in a clinical trial of RIC-SCT and two were unsure. This decision was again not influenced by any of the variables mentioned before.

Discussion

Apart from HU, the treatment of SCD is based on supportive elements with little progress having been made in medical management of this condition to improve life expectancy or QOL. Despite the encouraging results of allo-HSCT in SCD in younger patients, there has been scant attempt at making this treatment available to suitable young adults. The concern regarding conditioning-related toxicity in older patients is, indeed, relevant. However, van Besien *et al.*¹⁴ conducted a similar survey on 100 SCD patients from United States, regarding the acceptability of allo-HSCT and its related risks. sixty-three per cent were willing to take a risk of mortality over 5% in exchange for cure, with 15% willing to accept over 35% risk of TRM.¹⁴ Interestingly, there was no agreement between the health-care providers and the risk-acceptance of the patients, with most health-care providers unwilling to recommend the possibility of allo-HSCT to the majority of these patients.

The scenario is similar in our cohort. Ninety-three per cent were aware of allo-HSCT, but only 6% of patients had been informed about this procedure by their treating physicians. We carried out this survey as a pilot project exploring the risk-acceptance of allo-HSCT in an adult population with SCD. This was not limited to TRM but

also explored other long-term complications, in order to obtain a more holistic view about the attitude towards this procedure. With the advent of RIC, allo-HSCT now appears a realistic option for adults with SCD. One of the features of this form of allo-HSCT is a higher risk of GF, albeit with a possible reduction in mortality. GF following myeloablative conditioning would be incompatible with survival without intensive support or second transplantation, whereas in the era of RIC this is associated with autologous recovery and return to the original disease status. This is exemplified in a study from North America, where all the transplanted patients with SCD rejected the marrow following cessation of immunosuppression with return to HbSS status, with no morbidity or mortality.¹⁵ We have also explored this in our survey. The risk-acceptance for both TRM and GF was very high in this comparatively smaller cohort of adults with SCD. The acceptance of a higher risk was not prompted by more severe disease or failure of HU, as one may presume. It is interesting to note that patients less severely affected might opt for a risk-entailing therapy if it can offer a cure. This largely stems from the fact that, even with a disease which is less than severe in medical terms, SCD can still have a significant impact on QOL and social stereotyping. It is not unusual for a young adult to expect a healthy social life with security of employment and hence he might opt for a curative therapy to earn a fully productive life, rather than suboptimal living and a compromised lifestyle. In addition, the psycho-social issues related to SCD in young adults are often not apparent. One study from Nigeria highlighted the under diagnosis of depressive illness in this cohort.¹⁶ Suicidal ideas were reported to dominate during episodes of crisis. In another study from Europe over a 10-year period, four out of 61 deaths in SCD patients were related to suicide or refusal of care.¹⁷ These findings indicate that the acceptance of TRM in lieu of cure might vary with the underlying condition or adequacy of psychological support.

The other issues related to allo-HSCT that we explored, complement these findings. An attempt at cure may be

acceptable if the outcome is either death or a return to pre-transplant status in the worst scenario, but, it is surely not acceptable in exchange for another chronic debilitating condition, chronic GVHD; 80% of patients were not prepared to live with chronic GVHD even if it meant they were cured of SCD. This perception is very different from the sufferers of acute haematological malignancies who are offered allo-HSCT, where leukaemia-free survival may be exchanged for chronic morbidity.¹⁸ Another issue which stood out was that of infertility. This was unacceptable to most men within the constraints of small numbers, possibly reflecting the socio-cultural aspect of the study population. However, this survey did not include the possibility of different methods of fertility preservation in men and women.¹⁹ Semen cryopreservation is an accepted method of fertility preservation in men. It is possible that raising these issues could have moderated the opinion of some, if not all of the male participants. The issue of preservation of female fertility is still being developed and is not widely available under the National Health Service, but, oocyte or ovary cryopreservation methods are developing rapidly and might be considered an acceptable method of fertility preservation in the near future.

Thus, it is insufficient to devise a treatment to cure a chronic disease, which is compatible with several decades of survival, despite a severely compromised QOL. It is imperative that the feelings of the sufferers of a chronic disease are included when such allo-SCT protocols are devised. We had addressed these issues in a previous article when we reviewed the feasibility of allo-HSCT in adults with SCD and had proposed a RIC protocol and eligibility criteria.³ The conditioning incorporated Campath-1H in order to reduce chronic GVHD, but this may be at the cost of an increase in GF. We had also taken into account the issue of fertility in the conditioning regimen. Although these were more hypothetical propositions at that stage, our current survey emphasises its relevance in this setting. The suggested protocol had incorporated HU as preconditioning based on the theoretical proposition of reducing the severity of crises in the immediate peri-transplant period. A recent update of a Belgian study indeed argues in favour of this hypothesis.²⁰

Compliance with life-long treatment is a perceived problem in adults with SCD.²¹ However, in the backdrop of a cure, compliance with such treatment which is of paramount importance after an allo-HSCT might be much better, as evidenced in our study. Ninety-six per cent of the patients felt that they would be happy to comply with long-term medical treatment in context of a cure.

This is the first survey of its kind in an SCD population exploring the feelings and attitudes of this patient population towards possible RIC-SCT. The high acceptance rate of this procedure is not surprising, given the similar response to the survey in the United States which explored the attitude of patients with SCD towards the mortality associated with conventional allografting.¹⁴ Apparently, there is little impact of the health-care system on patient response if one compares these studies. One might expect a different attitude in private health insurance systems compared with a state-funded health economy. However, the universality of patient attitude underlines the fact that

the majority of sufferers of this condition would prefer a curative option rather than have supportive treatment for the rest of their life, irrespective of their geographical location. It was indeed encouraging that 60% of the participants expressed a willingness to participate in a clinical trial of RIC-SCT.

Availability of a family donor has often been raised as an issue with regard to transplantation in patients with SCD.^{22,23} However, this issue has not been revisited since the earlier studies. Our survey indicates that three-quarter of the patients in this cohort had a full sibling and in that case about 20% would be expected to have a matched family donor. A larger study is needed to explore the availability of family donors in the affected population in the UK.

This study once again emphasises the need to consider curative treatment for SCD where possible. Although arguments might be made in favour of conservative therapy, it is imperative that carefully controlled trials are undertaken to develop RIC-based allo-HSCT for SCD, so that patients can be offered a choice. The success of such a procedure would depend not only on offering a cure with reduced mortality but also addressing all the concerns raised by patients in this survey, in a constructive and sensitive manner.

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