

Review

THERAPEUTIC CHALLENGES IN CHILDHOOD SICKLE CELL DISEASE PART 2: A PROBLEM-ORIENTATED APPROACH

The major clinical problems arising in children with severe sickle cell disease are stroke, recurrent acute chest syndrome and frequent, debilitating vaso-occlusive crises. In the second part of this review, we aim to provide an evidence-based, problem-orientated approach to the current management of these problems in children. We review the risks and benefits for the various therapies available for each of these complications and provide evidence-based guidelines on their management.

INTRODUCTION

Sickle cell disease (SCD) is the commonest haemoglobinopathy and one of the commonest inherited diseases in the UK, affecting approximately 1 in 4000 live births every year in England (Hickman *et al.*, 1999). The most widely recognized complication is the painful crisis which accounts for over 90% of sickle-cell-related hospital admissions and is a significant cause of morbidity in these patients (Platt *et al.*, 1994). However, the most important causes of premature death and disability in SCD are the acute chest syndrome and sickle-related central nervous system (CNS) disease. Acute chest syndrome is the principal cause of mortality both in children and adults (Castro *et al.*, 1994; Platt *et al.*, 1994). Fatal chest syndrome has an incidence of 12.8 per 100 patient-years (Castro *et al.*, 1994) and accounts for approximately one-third of sickle-related deaths (Gray *et al.*, 1991). Acute chest syndromes often recur and may lead to long-term damage in the form of pulmonary fibrosis or chronic sickle cell lung disease (Powars *et al.*, 1988). Stroke is the most disabling complication of SCD and also a significant cause of death, accounting for about 6% of sickle-cell-related deaths (Gray *et al.*, 1991; Platt *et al.*, 1994). Approximately 10% of patients with SCD suffer from symptomatic infarction with paresis (Powars *et al.*, 1978; Ohene-Frempong *et al.*, 1998) and twice as many have been shown to have 'silent' infarction by modern neuroimaging techniques (Kinney *et al.*, 1999; Powars *et al.*, 1999; Pegelow *et al.*, 2002). If patients who have had a previous stroke are untreated, two-thirds will experience recurrence (Powars *et al.*, 1978).

Although improved management of the disease has prolonged survival in recent years (Lee *et al.*, 1995), even

in the developed world the median survival of homozygous patients has been estimated as 42 years for men and 48 years for women (Platt *et al.*, 1994). The mainstay of management is preventative and supportive care. The general management of SCD has been the subject of two excellent recent reviews (Castro, 1999; Steinberg, 1999). This review is the second of two parts; in *Part 1*, we reviewed the three principal current therapeutic modalities for childhood SCD [blood transfusion, hydroxyurea and bone marrow transplantation (BMT)] and potential future treatments. In *Part 2*, we aim to provide an evidence-based, problem-orientated approach to the current management of severe SCD in childhood, focusing on the three problems most prevalent in paediatric practice in developed countries: sickle-related CNS disease, recurrent acute chest syndrome and frequent, debilitating vaso-occlusive crises.

PROBLEM ORIENTATED APPROACH TO THE CHILD WITH SEVERE SCD: THE CHILD WITH STROKE AND/OR OTHER FORMS OF SICKLE-RELATED CNS DISEASE

Stroke occurs in up to 6% of patients with SCD (Powars *et al.*, 1978; Ohene-Frempong *et al.*, 1998) with a peak incidence of first stroke between the ages of 2–9 years and a second peak above the age of 30 years (Ohene-Frempong *et al.*, 1998). The real prevalence of cerebrovascular disease in these patients is even higher with subclinical lesions detected by magnetic resonance imaging (MRI) in around 22% of patients with SCD (Pegelow *et al.*, 2002). Many of these patients will not have reported symptoms but show reduced scores on formal neuropsychometric testing (Wang *et al.*, 2001). Patients who have suffered one stroke have an over 60% risk of recurrence if untreated (Powars *et al.*, 1978). Thus, the main two clinical problems are:

1. What is the best approach to preventing recurrence of stroke?
2. What is the best approach to preventing a first stroke in patients with evidence of occult CNS disease revealed by Doppler studies and/or MRI?

The options for management are: hydroxyurea, blood transfusion and BMT.

Hydroxyurea for sickle-related CNS disease in children

Although some studies have reported patients with previous stroke who have remained free of new neurological manifestations on hydroxyurea therapy (Ferster *et al.*, 2001), there is no convincing evidence that hydroxyurea reduces the risk of stroke in SCD. Indeed both primary and recurrent

strokes have been reported in children on hydroxyurea (Vichinsky & Lubin, 1994; Wang *et al.*, 2001). This may reflect the different pathogenetic mechanisms underlying the predominantly large vessel cerebrovascular occlusion seen in infarctive strokes compared with the microvascular occlusion seen in painful vaso-occlusive crises. In the only randomized, controlled study (Charache *et al.*, 1995), there was no difference in the incidence of stroke between hydroxyurea-treated and control patients. Ware *et al.* (1999) have reported a cohort of 16 children with SCD with previous stroke or transient ischaemic attacks (TIA), in whom hydroxyurea was substituted for transfusion therapy: three had recurrent strokes after a median follow-up of 22 months. Until prospective randomized studies are performed, hydroxyurea cannot be recommended as effective therapy for a child with SCD who has suffered a stroke. The available therapeutic options for such a child are, therefore, a chronic transfusion programme or allogeneic BMT.

The role of regular transfusions for sickle-related CNS disease in children

In children with SCD who have suffered a previous thrombotic stroke, a chronic, monthly transfusion programme aiming to keep HbS levels $\leq 30\%$ is effective at preventing further strokes in most children (Russell *et al.*, 1984; Pegelow *et al.*, 1995). There is no direct evidence that red cell transfusion confers effective secondary prevention for TIAs or after haemorrhagic stroke. Like most clinicians, we also recommend an exchange transfusion programme for these patients. The complications of regular transfusions, and the burden on the child and their family are often considerable. The principal problems are iron overload, red cell allo-immunization and transfusion-transmitted infections (Reisner *et al.*, 1987; Vichinsky *et al.*, 1990; Ballas, 2001; Vichinsky, 2001). Additional factors which limit the benefit of transfusion are: first, that strokes can recur even with regular transfusion. The prevalence of recurrent stroke in one multicentre retrospective analysis was 13% (Pegelow *et al.*, 1995). Second, it is unclear how long transfusion programmes for stroke should be continued and whether there is an identifiable stroke-free interval after which transfusions can safely be discontinued.

Initial reports showed an increased stroke rate soon after transfusions were stopped (Russell *et al.*, 1984; Wang *et al.*, 1991). By contrast, there were no recurrent strokes in a small group of patients in whom chronic transfusions were discontinued when they graduated from the paediatric to the adult clinic (Rana *et al.*, 1997). Because of this, clinical practice varies widely: many paediatric haematologists, particularly in the USA, recommend indefinite transfusion (Wang *et al.*, 1991), whereas others tend to stop after 5 years from the last stroke or at the age of 18 years. A recent study helped to identify a group of children in which it is likely that transfusions can be safely discontinued (Scothorn *et al.*, 2002). In a retrospective cohort study of 137 children with SCD on a chronic red cell transfusion programme for a minimum of 5 years, none of the 26 children whose initial stroke occurred in association with another medical event (e.g. acute chest

syndrome, hypertension, exchange transfusion) had another stroke during follow-up. By contrast, 31/111 (28%) of the children whose initial stroke occurred in the absence of an identifiable precipitating event had a second stroke; these strokes occurred despite the continuation of regular red cell transfusions, though at a lower rate than predicted in the absence of transfusion (Scothorn *et al.*, 2002). This study supports the view that indefinite transfusion (or BMT) is the best way we have at the moment to prevent recurrent stroke in children with SCD without a precipitating event for their first stroke. In those with a clear precipitating factor, consideration should be given to stopping transfusion therapy after a minimum of 3–5 years, depending on neurological status, imaging and issues relating to continued transfusion therapy. Further studies on the value of serial neurological imaging using state-of-the-art methods, including positron-emission tomography and MRI/magnetic resonance angiography (MRA), in children with SCD are needed to help address the question of the optimal duration of transfusion therapy and which children can be safely managed without long-term transfusion.

BMT for children with sickle-related CNS disease

In contrast to hydroxyurea and red cell transfusion, BMT remains the only therapy able to achieve long-term cure. Recurrence of stroke in patients with stable donor engraftment post BMT is rare and has only been reported in one patient (Bernaudin *et al.*, 1997). However in those with graft rejection, recurrent stroke remains a very real possibility (Walters *et al.*, 1996a). More recently, Walters *et al.* (2000) have evaluated CNS disease in 26 patients with at least 2 years of post-BMT follow-up, of whom 19 had clinical or radiological evidence of CNS abnormalities related to SCD prior to transplant. None of the 22 engrafted patients had SCD-related neurological events post BMT and the majority had stabilization or improvement of cerebral vasculopathy as assessed by MRI scans. Indeed, recent studies utilizing MRA have demonstrated improved cerebrovascular patency and reduced cerebral vessel blood flow rates post BMT (Steen *et al.*, 2001). Thus, in those who achieve stable donor engraftment, BMT appears effective in preventing stroke recurrence, though evaluation of larger numbers of patients with longer term follow-up will be needed to confirm the long-term value of this approach.

BMT versus transfusion for sickle-related CNS disease in children

No prospective, comparative studies have yet been performed to determine whether BMT or a regular transfusion programme results in superior overall or stroke-free survival in children with SCD who have suffered a stroke. Such studies have proved difficult to design and are likely only to be possible by comparing the long-term outcome in transplanted patients with well-matched, non-transplanted patients who lacked a human leucocyte antigen (HLA)-identical sibling donor. Without such data, our current approach is to offer BMT as an option to children who have

suffered a stroke, who have an HLA-identical sibling donor and who would otherwise be started on monthly red cell transfusions for a minimum of 3 years.

Faced with such a patient, a number of factors need to be considered, including patient and parental choice, co-morbidity both from the initial stroke and other complications of SCD which may increase the risks of transplant, and the age, health and wishes of the sibling. These factors have to be balanced against the availability of a safe blood supply and compliance with long-term transfusion and iron chelation. An initial period of chronic transfusion will always be needed in the aftermath of a stroke and this may provide a useful time to assess a child's compliance with a long-term transfusion protocol, including iron chelation, as well as their suitability for transplant. BMT offers a lower risk of stroke recurrence, a definitive cure and a good chance of an improved quality of life free from the unpredictable pattern of recurrent vaso-occlusive crises. On the other hand, BMT carries a higher early risk with treatment-related mortality of 6–8%, a 10% chance of graft rejection or chronic graft-versus-host disease and a high chance of infertility. In discussing these issues with patients and their families, physicians need to emphasize this balance between the potential for long-term cure with transplant at the cost of significant early risk compared with the relative safety of chronic transfusion but the need for long-term therapy and the possibility of stroke recurrence and other complications of SCD, particularly if transfusions are stopped.

The child with SCD and abnormal TCD studies

Primary stroke prevention is now possible in children with SCD. Patients at high risk of ischaemic stroke can be identified by abnormal cerebral blood velocity on transcranial doppler (TCD) studies of the internal carotid and middle cerebral arteries although, even in this group, 40% will never have a clinical stroke (Adams *et al*, 1992, 1998; Pegelow *et al*, 2001). In patients with an abnormal TCD who have not yet had a cerebrovascular accident (CVA), periodic blood transfusion appears highly effective in preventing stroke: in the first few years of the Stroke Prevention Trial in Sickle Cell Anemia (STOP) with a median follow-up of 21 months, there was only one stroke in 63 patients at high risk of CVA randomized to regular transfusion, compared with 11/67 children in the control group (Adams *et al*, 1998). Follow-up of these patients confirmed the benefit of transfusion and the prognostic value of abnormal TCD studies. However, the follow-up data also confirmed the failure of transfusions to prevent all strokes (there were three new strokes in transfused patients over a 28-month period of follow-up) and highlighted the practical difficulties of maintaining regular transfusions: one-third of patients elected to stop transfusions despite their apparent benefit and more than half of the patients were receiving iron chelation therapy for iron overload. However, it remains to be seen what proportion of those in the transfusion group will develop strokes in the long term and how long transfusion programmes are necessary in this group of patients. If late strokes are observed or long-term

transfusions are necessary, BMT may be a reasonable option for some of these patients. For the moment, however, we do not recommend BMT in this situation: a view supported by a recent decision analysis model, which showed no clear advantage to BMT over periodic blood transfusion in a hypothetical cohort of patients with SCD at risk of stroke because of abnormal cerebral blood velocity (Nietert *et al*, 2000).

THE CHILD WITH RECURRENT CHEST SYNDROME

Acute chest syndrome is the leading cause of death among patients with SCD, with an incidence of 12.8 per 100 patient years in the USA Co-operative Study (Castro *et al*, 1994). While exchange transfusion is the standard of care in severe acute chest syndrome, long-term studies of chronic transfusion for recurrent chest syndrome are not available (see *Part 1* of this review) and this approach has largely been superseded by the introduction of hydroxyurea. Therefore, the options for management of children with recurrent acute chest syndrome are hydroxyurea and BMT.

Hydroxyurea for recurrent acute chest syndrome

The role of hydroxyurea in preventing acute chest syndrome became apparent during the follow-up of patients enrolled in the Multicentre Study of Hydroxyurea in Sickle Cell Anaemia (MSH), a prospective, randomized trial involving 299 adult patients with SCD who were randomized to either hydroxyurea or placebo (Charache *et al*, 1995). The majority of patients in both arms of this study had a history of previous sickle chest syndrome. Nevertheless, significantly fewer patients assigned to hydroxyurea experienced sickle chest syndrome during the study (25 vs 51), although there was no significant reduction in mortality.

A prospective, randomized study of hydroxyurea versus placebo similar to the MSH study is needed to assess its efficacy in children. In the absence of such a trial, however, the clinical benefit and short-term safety of hydroxyurea has now been addressed in a number of phase I/II studies in children (Jayabose *et al*, 1996; Kinney *et al*, 1999; Ferster *et al*, 2001). It is clear that hydroxyurea improves haemoglobin and HbF levels at least as effectively as in adults (see *Part 1* of this review). In addition, although these trials were neither randomized nor controlled, in the two trials in which it was evaluated, there was a reduction in the frequency of vaso-occlusive crises and chest syndrome compared with pretreatment (Koren *et al*, 1999; Ferster *et al*, 2001). As with adults, some children on hydroxyurea did experience recurrence of these symptoms (Jayabose *et al*, 1996; Ferster *et al*, 2001). Data from these studies also suggest that treatment of children with SCD with hydroxyurea is safe, at least in the short term: the most common problem being reversible myelotoxicity (Halsey & Roberts, 2003). However, further studies will be needed to determine the recurrence rate of chest syndrome while on hydroxyurea, as well as the long-term effects, particularly potential oncogenicity.

The role of BMT in the management of recurrent acute chest syndrome

BMT is certainly effective in preventing recurrence of acute chest syndrome. In the Seattle late-effects cohort, no patient, including eight transplanted for recurrent acute chest syndrome, experienced acute chest syndrome post BMT (Walters *et al.*, 2000). Seven of the eight patients with prior chest syndrome had stable pulmonary function during the period of follow-up. Overall, 21 out of 26 patients had stable or normal pulmonary function, one patient died of obliterative bronchiolitis related to chronic graft-versus-host disease (GVHD) and two patients experienced a decline in respiratory function in the absence of GVHD. Thus, engrafted patients appear to be no longer at major risk of acute chest syndrome and in the majority of patients there does not appear to be a significant early pulmonary toxicity from busulphan in SCD patients (Walters *et al.*, 1996a; Walters *et al.*, 2000).

Longitudinal comparisons of the incidence of recurrent chest syndrome and pulmonary function in patients treated with hydroxyurea compared with those undergoing BMT are needed to determine the optimal therapeutic modality for SCD patients with chest complications. When deciding which therapeutic modality is appropriate for a child with recurrent chest syndrome, physicians need to balance the possibility of recurrence of acute chest syndrome and other complications of SCD while on hydroxyurea, as well as the potential for oncogenicity, against the treatment-related mortality and late effects of BMT. It is clear that hydroxyurea, when properly monitored, is safe and, by extension from studies of its use in patients with polycythaemia, if there is a risk of leukaemogenesis this is likely to be very low (reviewed in Halsey & Roberts, 2003). Further, there is evidence that the natural history of acute chest syndrome is one of decreasing incidence as children get older, even when analysed on a within-person basis (Castro *et al.*, 1994). This supports a relatively conservative approach in the hope that time will ameliorate the course of the disease and that hydroxyurea will only be needed for a finite period. An important caveat is that the morbidity and mortality of acute chest syndrome increases with age (Vichinsky *et al.*, 2000) and, whichever mode of treatment is chosen, the prime objective is to prevent this complication developing. On balance, then, a trial of hydroxyurea in the first instance would seem prudent for children with recurrent chest syndrome, reserving BMT for those in whom hydroxyurea fails or cannot be tolerated.

THE CHILD WITH RECURRENT PAINFUL CRISES

Hydroxyurea for recurrent vaso-occlusive crises

As discussed in *Part 1* of this review, evidence for the efficacy of hydroxyurea in patients with recurrent painful crises is compelling. The MSH study established that hydroxyurea significantly reduced the annual rates of vaso-occlusive crises and hospitalization in adults compared with placebo (Charache *et al.*, 1995). Although no randomized, controlled trials have been performed in children, a number of studies have demonstrated a reduction in the

frequency of painful crises in children treated with hydroxyurea (Jayabose *et al.*, 1996; Maier-Redelsperger *et al.*, 1999; Ferster *et al.*, 2001). While clearly effective in SCD, hydroxyurea is not curative. Many patients continue to have painful crises and the response to hydroxyurea is difficult to predict in an individual patient; close monitoring is required to prevent myelotoxicity and, although the risk is likely to be low, mutagenicity associated with long-term use remains possible (Halsey & Roberts, 2003). Nonetheless, in patients with recurrent painful crises sufficiently severe to require specific therapy, the balance of risks versus benefit favours hydroxyurea over other therapeutic options and an initial trial of this drug should be the treatment of choice. While a number of baseline laboratory parameters may predict the response to hydroxyurea at the population level (Ware *et al.*, 2002), these parameters should not be used in deciding whether a trial of hydroxyurea is indicated for an individual patient. As the beneficial effects of hydroxyurea might not become manifest for several months, we would recommend at least a 6-month trial in the first instance.

Transfusion therapy for children with recurrent vaso-occlusive crises

There are no randomized studies assessing the efficacy of transfusion in preventing painful crises in children. The strongest evidence for this approach comes from a randomized study in pregnant women with SCD (Koshy *et al.*, 1988), in which a prophylactic transfusion programme significantly reduced the rate of vaso-occlusive crises. Whether, these findings can be extrapolated to children with severe disease is unclear. Additionally, the available evidence suggests that the risks associated with a chronic transfusion programme are likely to be greater than those associated with hydroxyurea when adequately monitored: whereas no patient on either the MSH study (Charache *et al.*, 1995) or the in the paediatric studies (Kinney *et al.*, 1999) experienced major toxicity, chronic transfusion is associated with difficulties of vascular access, and a high risk of development of allo-antibodies and iron overload (Ballas, 2001; Vichinsky, 2001). Finally, treatment with hydroxyurea involves less disruption of a child's lifestyle than a transfusion programme. Transfusion programmes should thus be reserved for children who have failed or been intolerant of a trial of hydroxyurea and for whom BMT is not an option (see below).

BMT for recurrent vaso-occlusive crises

BMT is certainly effective at preventing recurrent painful crises. In the three major series of patients transplanted for SCD (Bernaudin *et al.*, 1997; Vermylen *et al.*, 1998; Walters *et al.*, 2000), no patient with stable engraftment has had recurrence of vaso-occlusive crises. In the 10–18% of patients with rejection/autologous reconstitution, recurrent painful crises often recur, but even in some of these the course of disease may be ameliorated for several years (Ferster *et al.*, 1995). This benefit needs to be balanced against a transplant-related mortality of 6–8%, the likelihood of impaired fertility (at least with current conditioning regimens) and a 4–8% risk of extensive chronic GVHD.

Given the less life-threatening nature of this situation compared with stroke or recurrent chest crises, we feel that the risks of BMT do not justify its use as first-line therapy in a child with recurrent painful crises. We propose that, like chronic transfusion, BMT should be reserved for children in whom life is most severely disrupted and who have either not responded to or been intolerant of hydroxyurea. In such patients, the choice between these secondary therapeutic modalities should take into account a number of factors, including patient and parent choice, co-morbidity, the availability of a matched sibling donor, the availability of a safe blood supply and the likelihood of compliance with a transfusion/chelation programme. In the majority of patients who do not have a matched sibling donor (Walters *et al.*, 1996b), the choice is a simple one. In those with a donor, if other considerations are equal, an initial trial of transfusion, as the more conservative therapy, to assess its efficacy at ameliorating the symptoms and compliance may help parents and physicians to decide between these modalities.

CONCLUSIONS

The complications of childhood SCD that most often give rise to management problems are stroke, recurrent acute chest syndrome and frequent, painful, debilitating vaso-occlusive crises. While recent advances in our understanding of the pathogenesis of vascular occlusion in SCD have led to novel pharmacological strategies (Rosse *et al.*, 2000), BMT remains the only curative modality for those with severe disease. The availability of a matched sibling donor remains a major barrier to the broader application of BMT for SCD (Walters *et al.*, 1996b), and transplantation with alternative sources of stem cells and/or non-myeloablative conditioning regimens should be rigorously evaluated (see *Part 1*).

For children who have suffered a stroke, the treatment options are BMT or regular red cell transfusions for a minimum of 3 years. Given the outcome of BMT in this setting ($\geq 80\%$ long-term cure) (Walters *et al.*, 2000), BMT should be offered to all such children who have an HLA-identical donor. However, both BMT and regular transfusion are reasonable options and the choice will depend on the individual child. In discussing this choice with patients and their families, physicians need to emphasize the balance between the potential for long-term cure with BMT at the cost of significant early risks, compared with the relative safety of chronic transfusion but the need for long-term therapy and the possibility of stroke recurrence and other complications of SCD, particularly if transfusions are stopped. It is now appropriate to consider randomized, controlled clinical trials comparing the risks and benefits of these two therapeutic modalities for patients with preceding stroke, ideally with randomization by donor availability.

For children with recurrent acute chest syndrome due to SCD, the choice of treatment lies between hydroxyurea and BMT. Here, the physician needs to balance the possibility of recurrence of acute chest syndrome and other complications of SCD while on hydroxyurea, as well as its potential

oncogenicity, against the treatment-related mortality and possible late effects of BMT. As the natural history of acute chest syndrome is one of decreasing incidence as children get older, a conservative approach with a trial of hydroxyurea in the first instance would seem prudent in this situation, reserving BMT for those in whom hydroxyurea fails or cannot be tolerated.

Lastly, for the child with recurrent painful crises, the evidence base for the efficacy of hydroxyurea is compelling and this should be the treatment of choice. Transfusion programmes are less desirable, both because of relatively limited data on efficacy and more toxicity, as well as more disruption to the child's lifestyle. Given the less life-threatening nature of this situation compared with stroke or recurrent chest crises, BMT should be reserved for patients in whom life is most severely disrupted who have either not responded to or been intolerant of hydroxyurea.

Finally, it should be acknowledged that, for the majority of children with SCD, i.e. those living in under-resourced countries, the therapeutic modalities outlined in this review will never be available. For these children, the first aims must be to put in place the most basic measures to combat poverty, improve nutrition and prevent infection at the same time as working towards programmes for screening and safe transfusion.

¹Department of Bone Marrow Transplantation, Great Ormond Street Hospital for Sick Children, PERSIS J. AMROLIA¹
ANTONIO ALMEIDA²
SALLY C. DAVIES³
²Department of Haematology, Imperial College Faculty of Medicine, and ³Department of Haematology, Central Middlesex Hospital, London, UK IRENE A. G. ROBERTS²

REFERENCES

- Adams, R., McKie, V., Nichols, F., Carl, E., Zhang, D.L., McKie, K., Figueroa, R., Litaker, M., Thompson, W. & Hess, D. (1992) The use of transcranial ultrasonography to predict stroke in sickle cell disease. *New England Journal of Medicine*, **326**, 605–610.
- Adams, R.J., McKie, V.C., Hsu, L., Files, B., Vichinsky, E., Pegelow, C., Abboud, M., Gallagher, D., Kutlar, A., Nichols, F.T., Bonds, D.R. & Brambilla, D. (1998) Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *New England Journal of Medicine*, **339**, 5–11.
- Ballas, S.K. (2001) Iron overload is a determinant of morbidity and mortality in adult patients with sickle cell disease. *Seminars in Hematology*, **38**, 30–36.
- Bernaudin, F., Souillet, G., Vannier, J.P., Vilmer, G., Michel, G., Lutz, P., Pouvier, E., Bordigoni, P., Margueritte, G., Kuentz, M. & Vernant, J.P. (1997) Report of the French experience concerning 26 children transplanted for severe sickle cell disease. *Bone Marrow Transplantation*, **19**, 112–115.
- Castro, O. (1999) Management of sickle cell disease: recent advances and controversies. *British Journal of Haematology*, **107**, 2–11.
- Castro, O., Brambilla, D.J., Thorington, B., Reindorf, C.A., Scott, R.B., Gillette, P., Vera, J.C. & Levy, P.S. (1994) The acute chest

- syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. *Blood*, **84**, 643–649.
- Charache, S., Terrin, M.L., Moore, R.D., Dover, G.J., Barton, F.B., Eckert, S.V., McMahon, R.P. & Bonds, D.R. (1995) Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *New England Journal of Medicine*, **332**, 1317–1322.
- Ferster, A., Corazza, F., Vertongen, F., Bujan, W., Devalck, C., Fondou, P., Cochaux, P., Lambermont, M., Khaladji, Z. & Sariban, E. (1995) Transplanted sickle-cell disease patients with autologous bone marrow recovery after graft failure develop increased levels of fetal haemoglobin which corrects disease severity. *British Journal of Haematology*, **90**, 804–808.
- Ferster, A., Tahiri, P., Vermyn, C., Sturbois, G., Corazza, F., Fondou, P., Devalck, C., Dresse, M.F., Feremans, W., Hunnink, K., Toppet, M., Philippet, P., Van Geet, C. & Sariban, E. (2001) Five years of experience with hydroxyurea in children and young adults with sickle cell disease. *Blood*, **97**, 3628–3632.
- Gray, A., Anionwu, E.N., Davies, S.C. & Brozovic, M. (1991) Patterns of mortality in sickle cell disease in the United Kingdom. *Journal of Clinical Pathology*, **44**, 459–463.
- Halsey, C. & Roberts, I.A.G. (2003) The role of hydroxyurea in sickle cell disease. *British Journal of Haematology* (in press).
- Hickman, M., Modell, B., Greengross, P., Chapman, C., Layton, M., Falconer, S. & Davies, S.C. (1999) Mapping the prevalence of sickle cell and beta thalassaemia in England: estimating and validating ethnic-specific rates. *British Journal of Haematology*, **104**, 860–867.
- Jayabose, S., Tugal, O., Sandoval, C., Patel, P., Puder, D., Lin, T. & Visintainer, P. (1996) Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. *Journal of Pediatrics*, **129**, 559–565.
- Kinney, T.R., Helms, R.W., O'Branski, E.E., Ohene-Frempong, K., Wang, W., Daeschner, C., Vichinsky, E., Redding-Lallinger, R., Gee, B., Platt, O.S. & Ware, R.E. (1999) Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Pediatric Hydroxyurea Group. *Blood*, **94**, 1550–1554.
- Koren, A., Segal-Kupershmit, D., Zalman, L., Levin, C., Abu, H.M., Palmor, H., Luder, A. & Attias, D. (1999) Effect of hydroxyurea in sickle cell anemia: a clinical trial in children and teenagers with severe sickle cell anemia and sickle cell beta-thalassaemia. *Pediatric Hematology and Oncology*, **16**, 221–232.
- Koshy, M., Burd, L., Wallace, D., Moawad, A. & Baron, J. (1988) Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. *New England Journal of Medicine*, **319**, 1447–1452.
- Lee, A., Thomas, P., Cupidore, L., Serjeant, B. & Serjeant, G. (1995) Improved survival in homozygous sickle cell disease: lessons from a cohort study. *British Medical Journal*, **311**, 1600–1602.
- Maier-Redelsperger, M., Labie, D. & Elion, J. (1999) Long-term hydroxyurea treatment in young sickle cell patients. *Current Opinions in Hematology*, **6**, 115–120.
- Nietert, P.J., Abboud, M.R., Silverstein, M.D. & Jackson, S.M. (2000) Bone marrow transplantation versus periodic prophylactic blood transfusion in sickle cell patients at high risk of ischemic stroke: a decision analysis. *Blood*, **95**, 3057–3064.
- Ohene-Frempong, K., Weiner, S.J., Sleeper, L.A., Miller, S.T., Embury, S., Moehr, J.W., Wethers, D.L., Pegelow, C.H. & Gill, F.M. (1998) Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*, **91**, 288–294.
- Pegelow, C.H., Adams, R.J., McKie, V., Abboud, M., Berman, B., Miller, S.T., Olivieri, N., Vichinsky, E., Wang, W. & Brambilla, D. (1995) Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. *Journal of Pediatrics*, **126**, 896–899.
- Pegelow, C.H., Wang, W., Granger, S., Hsu, L.L., Vichinsky, E., Moser, F.G., Bello, J., Zimmerman, R.A., Adams, R.J. & Brambilla, D. (2001) STOP trial: silent infarcts in children with sickle cell anemia and abnormal cerebral artery velocity. *Archives of Neurology*, **58**, 2017–2221.
- Pegelow, C.H., Macklin, E.A., Moser, F.G., Wang, W.C., Bello, J.A., Miller, S.T., Vichinsky, E.P., DeBaun, M.R., Guarini, L., Zimmerman, R.A., Younkin, D.P., Gallagher, D.M. & Kinney, T.R. (2002) Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. *Blood*, **99**, 3014–3018.
- Platt, O.S., Brambilla, D.J., Rosse, W.F., Milner, P.F., Castro, O., Steinberg, M.H. & Klug, P.P. (1994) Mortality in sickle cell disease. Life expectancy and risk factors for early death. *New England Journal of Medicine*, **330**, 1639–1644.
- Powars, D., Wilson, B., Imbus, C., Pegelow, C. & Allen, J. (1978) The natural history of stroke in sickle cell disease. *American Journal of Medicine*, **65**, 461–471.
- Powars, D., Weidman, J.A., Odom-Maryon, T., Niland, J.C. & Johnson, C. (1988) Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. *Medicine (Baltimore)*, **67**, 66–76.
- Powars, D.R., Conti, P.S., Wong, W.Y., Groncy, P., Hyman, C., Smith, E., Ewing, N., Keenan, R.N., Zee, C.S., Harold, Y., Hiti, A.L., Teng, E.L. & Chan, L.S. (1999) Cerebral vasculopathy in sickle cell anemia: diagnostic contribution of positron emission tomography. *Blood*, **93**, 71–79.
- Rana, S., Houston, P.E., Surana, N., Shalaby-Rana, E.I. & Castro, O.L. (1997) Discontinuation of long-term transfusion therapy in patients with sickle cell disease and stroke. *Journal of Pediatrics*, **131**, 757–760.
- Reisner, E.G., Kostyu, D.D., Phillips, G., Walker, C. & Dawson, D.V. (1987) Alloantibody responses in multiply transfused sickle cell patients. *Tissue Antigens*, **30**, 161–166.
- Rosse, W.F., Narla, M., Petz, L.D. & Steinberg, M.H. (2000) New views of sickle cell disease pathophysiology and treatment. *Hematology 2000 (American Society of Hematology Educational Program)*, 2–17. American Society of Hematology, Washington DC.
- Russell, M.O., Goldberg, H.I., Hodson, A., Kim, H.C., Halus, J., Reivich, M. & Schwartz, E. (1984) Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. *Blood*, **63**, 162–169.
- Scothorn, D.J., Price, C., Schwartz, D., Terrill, C., Buchanan, G.R., Shurney, W., Sarniak, I., Fallon, R., Chu, J.Y., Pegelow, C.H., Wang, W., Casella, J.F., Resar, L.S., Berman, B., Adamkiewicz, T., Hsu, L.L., Ohene-Frempong, K., Smith-Whitley, K., Mahoney, D., Scott, J.P., Woods, G.M., Watanabe, M. & Debaun, M.R. (2002) Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke. *Journal of Pediatrics*, **140**, 348–354.
- Steen, R.G., Helton, K.J., Horwitz, E.M., Benaim, E., Thompson, S., Bowman, L.C., Krance, R., Wang, W.C. & Cunningham, J.M. (2001) Improved cerebrovascular patency following therapy in patients with sickle cell disease: initial results in 4 patients who received HLA-identical hematopoietic stem cell allografts. *Annals of Neurology*, **49**, 222–229.
- Steinberg, M.H. (1999) Management of sickle cell disease. *New England Journal of Medicine*, **340**, 1021–1030.
- Vermyn, C., Cornu, G., Ferster, A., Brichard, B., Ninane, J., Ferrant, A., Zenebergh, A., Maes, P., Dhooge, C., Benoit, Y.,

- Beguín, Y., Dresse, M.F. & Sariban, E. (1998) Haematopoietic stem cell transplantation for sickle cell anaemia: the first 50 patients transplanted in Belgium. *Bone Marrow Transplantation*, **22**, 1–6.
- Vichinsky, E. (2001) Current issues with blood transfusion in sickle cell disease. *Seminars in Hematology*, **38**, 14–22.
- Vichinsky, E.P. & Lubin, B.H. (1994) A cautionary note regarding hydroxyurea in sickle cell disease. *Blood*, **83**, 1124–1128.
- Vichinsky, E.P., Earles, A., Johnson, R.A., Hoag, M.S., Williams, A. & Lubin, B. (1990) Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. *New England Journal of Medicine*, **322**, 1617–1621.
- Vichinsky, E., Neumayr, L.D., Earles, A.N., Williams, R., Lennette, E.T., Dean, D., Nickerson, B., Orringer, E., McKie, V., Bellevue, R., Daeschner, C., Mancini-Gardner, E., Abboud, M., Moncino, M., Ballas, S. & Ware, R. (2000) Causes and outcome of the acute chest syndrome in sickle cell disease. *New England Journal of Medicine*, **342**, 1855–1865.
- Walters, M.C., Patience, M., Leisenring, W., Eckman, J.R., Scott, J.P., Mentzer, W.C., Davies, S.C., Ohene-Frempong, K., Bernaudin, F., Matthews, D.C., Storb, R. & Sullivan, K.M. (1996a) Bone marrow transplantation for sickle cell disease. *New England Journal of Medicine*, **335**, 369–376.
- Walters, M.C., Patience, M., Leisenring, W., Eckman, J.R., Buchanan, G.R., Rogers, Z.R., Olivieri, N.F., Vichinsky, E., Davies, S.C., Mentzer, W.C., Powars, D., Scott, J.P., Bernaudin, F., Ohene-Frempong, K., Darbyshire, P.J., Wayne, A., Roberts, I.A.G., Dindorf, P., Brandalise, S., Sanders, J.E., Matthews, D.C., Appelbaum, F.R., Storb, R. & Sullivan, K.M. (1996b) Barriers to bone marrow transplantation for sickle cell anemia. *Biology of Blood and Marrow Transplantation*, **2**, 100–104.
- Walters, M.C., Storb, R., Patience, M., Leisenring, W., Taylor, T., Sanders, J.E., Buchanan, G.E., Rogers, Z.R., Dinndorf, P., Davies, S.C., Roberts, I.A., Dickerhoff, R., Yeager, A.M., Hsu, L., Kurtzberg, J., Ohene-Frempong, K., Bunin, N., Bernaudin, F., Wong, W.Y., Scott, J.P., Margolis, D., Vichinsky, E., Wall, D.A., Wayne, A.S., Pegelow, C., Redding-Lallinger, R., Wiley, J., Klemperer, M., Mentzer, W.C., Smith, F.O. & Sullivan, K.M. (2000) Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. *Blood*, **95**, 1918–1924.
- Wang, W.C., Kovnar, E.H., Tonkin, I.L., Mulhern, R.K., Langston, J.W., Day, S.W., Schell, M.J. & Wilimas, J.A. (1991) High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease. *Journal of Pediatrics*, **118**, 377–382.
- Wang, W.C., Wynn, L.W., Rogers, Z.R., Scott, J.P., Lane, P.A. & Ware, R.E. (2001) A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *Journal of Pediatrics*, **139**, 790–796.
- Ware, R.E., Zimmerman, S.A. & Schultz, W.H. (1999) Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with SCD. *Blood*, **94**, 3022–3026.
- Ware, R.E., Eggleston, B., Redding-Lallinger, R., Wang, W.C., Smith-Whitley, K., Daeschner, C., Gee, B., Styles, L.A., Helms, R.W., Kinney, T.R. & Ohene-Frempong, K. (2000) Predictors of fetal hemoglobin response in children with sickle cell anemia receiving hydroxyurea therapy. *Blood*, **99**, 10–14.
- Ware, R.E., Eggleston, B., Redding-Lallinger, R., Wang, W.C., Smith-Whitley, K., Daeschner, C., Gee, B., Styles, L.A., Helms, R.W., Kinney, T.R. & Ohene-Frempong, K. (2002) Predictors of fetal hemoglobin response in children with sickle cell anemia receiving hydroxyurea therapy. *Blood*, **99**, 10–14.

Keywords: sickle cell disease, chest crisis, vaso-occlusive crisis, stroke, hydroxyurea.