

ORIGINAL ARTICLE

Fanconi anaemia: new strategies

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Fanconi anaemia (FA) is a rare genetic disease characterized by chromosomal instability, somatic abnormalities, marrow failure and cancer proness. The main cause of morbidity and mortality is bone marrow failure, which typically arises in the first decade of life and progresses to full-blown transfusion dependence and severe neutropenia in a variable number of years. Myelodysplastic syndrome (MDS) and AML may arise on the background of marrow failure, although cases of patients diagnosed with MDS or overt leukaemia before the full appearance of marrow aplasia are reported. This article reviews the current options for treatment of bone marrow failure in FA and provides an algorithm for supporting decisions on treatment. The use of androgens, corticosteroids and growth factors is reviewed, as well as the results in recent cohorts of matched sibling donor haematopoietic stem cell (HSC) transplants and unrelated donor HSC transplants, including cord blood graft. The conditioning regimens used are analysed and commented. Up-to-date information on second tumours after HSC transplant and on experimental treatments such as gene therapy, prenatal and preimplantation diagnosis and inhibition of pro-inflammatory cytokines is provided.

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Introduction

Fanconi anaemia (FA) is a rare genetic disease characterized by chromosomal instability, somatic abnormalities, marrow failure and a tendency to develop haematological and non-haematological malignancies. Thirteen complementation groups and 12 genes (FANCA, B, C, D1, D2, E, F, G, J, L, M, PALB 2)^{1,2} have now been identified encoding proteins that are involved in a number of cellular functions including DNA repair, Re-dox, cytokine regulation and apoptosis.³ Even if FA patients may suffer from non-haematological complications such as solid tumours or

somatic malformations, marrow failure still remains the main cause of mortality and morbidity.

Usually, marrow failure appears between 5 and 10 years of age and invariably progresses with variable speed to the exhaustion of the haematopoietic stem cells (HSCs), which corresponds to the stage of full transfusion dependence and severe neutropenia. Myelodysplastic syndrome (MDS) and AML may arise on the background of marrow failure, although cases of patients diagnosed with MDS or overt leukaemia before the full appearance of the aplastic phase, aplasia, are reported.

Even if intimate mechanisms leading to the depletion of the marrow stem cells are not fully clarified, recent studies importantly contributed to the understanding of the pathogenesis of haematopoietic failure in FA. The review of the biological pathways capable of causing marrow failure in FA is beyond the scope of this article; however, increasing evidence, both in humans⁴ and in mice models,^{5,6} supports the theory that FA marrow failure derives from increased apoptosis due to excess sensitivity to inflammatory cytokines such as tumour necrosis factor- α (TNF- α) and IFN- γ , and reactive oxygen species. Noteworthy, TNF- α in FANCC mice may also increase chromosomal aberrations⁶ and impair oxidative DNA-damage repair, thus implying a tight link between inflammation, reactive oxygen species and DNA damage. This may open new scenarios in the relationship between inflammation and pre-cancer diseases.

Current options for treatment of marrow failure

So far, the only option capable of restoring acceptable levels of long-term haematopoiesis is haematopoietic stem cell transplantation (HSCT). In this article, the various treatment options will be reviewed. An algorithm for supporting treatment decisions on marrow failure of FA patients will be provided in the final section and in Figure 1.

Androgens and corticosteroids

FA patients offer some response to androgens if this treatment is started in a not-too-advanced stage, that is, when some residual autologous haematopoiesis is left.

About 75% of patients respond to androgens. The response is often slow (within 2–12 months), incomplete (haemoglobin generally does better than neutrophils and platelets) and generally drug dependent. Overall survival is better in androgen-treated (20 years) vs non-treated

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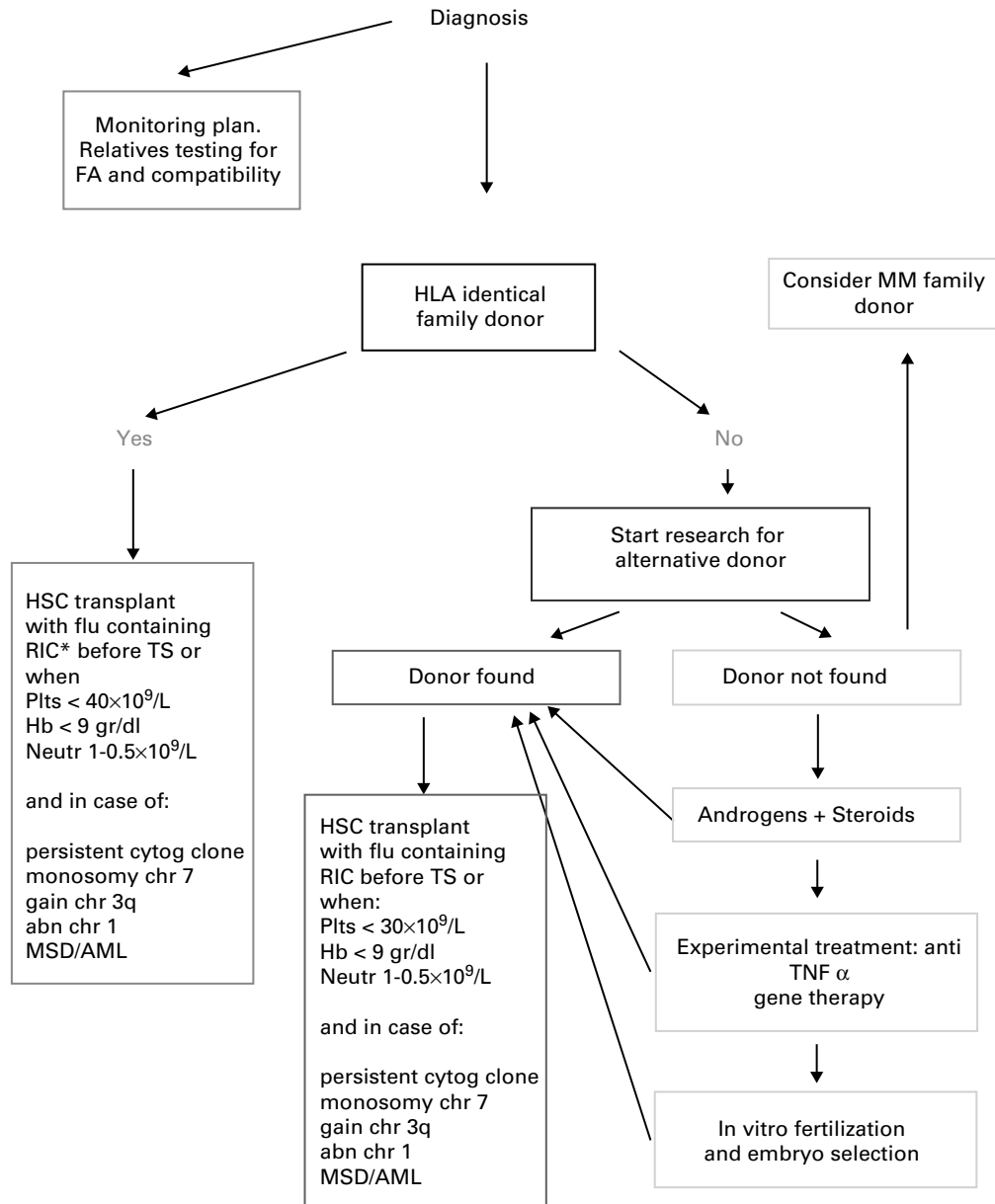


Figure 1 Algorithm for treatment decisions. RIC, reduced intensity.

patients (14 years). Recommended drug is oxymetholone at the dose of 2–5 mg/kg/day to be modulated on the level of response but not to be discontinued. The combination with prednisolone 2 mg/kg/day reduces the risk of liver toxicity. Side effects include masculinization, final short stature, peliosis hepatis, liver adenomas and hepatocellular carcinomas.⁷ Androgens were reported to adversely affect the outcome of subsequent HSCT in some studies⁸ but not in others.⁹ Overall, androgens can be considered in the absence of a suitable marrow donor, when some residual haematopoiesis is still present but not as a definitive long-term treatment.

Corticosteroids in combination with androgens may help to minimize their dosage, but if used alone they do not have a place in the treatment of marrow failure of FA patients.

Growth factors

EPO, G-CSF, GM-CSF and IL-3 have been tried in limited numbers of FA patients. Responses were partial and transient.⁷ Although not formally proven, there is more than one concern that growth factors can accelerate the development of clonal haematopoiesis (MDS/AML). At present, they do not represent a concrete option in the long term. In the short term and in neutropenic patients, G-CSF may have a place in the case of acute infections to facilitate their clearance by antibiotics.

HSCT from matched sibling donors

If a non-FA, HLA-identical relative is available in the family, then HSCT from matched sibling donor is the first-choice treatment for marrow failure. The time of transplant

Table 1 Results of HSC transplants from matched related donor over the last 6 years in FA

	<i>Tan et al.</i> ¹⁴ (11 patients)	<i>Dufour et al.</i> ¹² (27 patients)	<i>Zanis-Neto et al.</i> ¹¹ (30 patients)	<i>Farzin et al.</i> ¹³ (35 patients)
Conditioning regimen	LDCY + FLU + ATG pre ^a	TAI/TBI 500 cGy + LDCY 22 patients HDCY 5 patients	INTCY 60–80 mg	TAI/TBI 400 cGy + LDCY ATG pre and post
Graft failure	9%	8%	0%	5.7%
Acute GvHD \geq grade 2	0 ^b	36%	13–57%	14.2%
Chronic GvHD	0 ^b	12.5%	14–50%	12%
TRM	9%	18.5%	4.3–42%	8.5%
Late tumour		0	9.67% ^c	5.7%
Follow-up	2.9 years	3 years	1.2–4 years	10 years
Overall actuarial survival	82%	83.5%	88–57%	83%

Abbreviations: HDCY = high-dose cyclophosphamide = 120 mg/kg; HSC = haematopoietic stem cell; FA = Fanconi anaemia; INTCY = intermediate-dose cyclophosphamide = 60–80 mg/kg; LDCY = low-dose cyclophosphamide = 20 mg/kg.

^aT-cell-depleted bone marrow cells or unmanipulated umbilical cord blood cells were infused.

^bAc GVHD and chronic GVHD occurred in two patients who were re-transplanted, respectively, for Graft failure and MDS relapse.

^cSecond tumours occurred in 6/62 previously transplanted patients reported in the same article 4.7–11.8 years after the transplant. These patients were conditioned with CY 200 mg/kg (5 patients) and CY 140 mg/kg (1 patient).

is when transfusion dependence is pending, better if no or minimal transfusions have been performed. Also the appearance of persistent cytogenetic clone, abnormalities of chromosome 1, 3 or 7 or MDS/AML indicate the transplant. Over time, two conditioning regimens were used. The first, adopted by the Eliane Gluckman team at St Louis in Paris,¹⁰ included low-dose CY (20–40 mg/kg) plus TAI/TBI (400–450 cGy). The other, used by the Seattle group, employed CY as a single agent at increased doses (200–100 mg/kg), which were effective for engraftment but burdened by high toxicity, and for this reason they were progressively reduced to 60–80 mg/kg.¹¹

Both types of conditioning regimens provided good results. As detailed in Table 1,^{11–13} actuarial overall survival ranged between 83 and 88% with a TRM of 8–18.5%, highest failure rate of 8% and average chronic GVHD around 12%. Ac GvHD peaked to 36% in one study¹² and, along with TRM and chronic Ac GvHD, was remarkably high also in a small group of patients conditioned only with CY 80 mg/kg.¹¹ Of note is that GvHD, in addition to negatively impacting on survival and quality of life, is one of the major risk factors for the development of late tumours.^{15,16}

Over the recent years, fludarabine (Flu)-containing reduced-intensity conditioning regimens have become more popular and are being successfully employed also in FA. In a recently published cohort of 11 patients,¹⁴ actuarial overall survival was 82%, TRM was 9%, GvHD was negligible and toxicity, on the whole, low. There are no published studies with longer follow-up and far greater number of patients transplanted with Flu-based preparative regimen. However, also given the results obtained in the unrelated donor transplant setting, it seems likely that conditioning regimens containing Flu and low-dose CY will turn out to provide at least as equivalent survival rates as those with low-dose CY + TAI or intermediate-dose CY (80–60 mg/kg), but at the cost of a lower GvHD and early/late complication rates. Flu, as a fluorinated purine analogue, does not act as a crosslinking agent. In theory, this might contribute to reduce the risk of late malignancies.

In the case of FA patients with clonal haematopoiesis or overt MDS/AML, this reduced-intensity approach may not be sufficient and stronger preparative regimens may be required.

HCST from alternative donors

The genetic nature of the disease unfortunately reduces the chances of finding a healthy matched family donor, and this addresses many expectations of successful treatments towards alternative donor transplants. In the past decades, the outcome of alternative or unrelated donor transplants in FA was clearly discouraging mainly because of high risk of TRM, which in turn was due to graft failure, Ac GvHD, infections and excessive conditioning regimen-organ-related toxicity.

The recent literature available on HSCT from alternative donors reports on important ameliorations after the introduction of Flu-based conditioning regimens. Flu, by virtue of its profound immunosuppressive effect, has improved engraftment without increasing the risk of toxicity. In the pre-Flu era, overall survival was dramatically down to around 30%,^{8,10} but with the introduction of this agent, it has remarkably increased to 53%¹⁷ with a top percentage of 96.¹⁸

TRM, which in alternative donor HSCT historically had rates of about 70–80%, in the largest study ever performed on alternative donor transplants in FA,¹⁷ has remarkably declined from 81 to 47% with the use of Flu. The same study reports a significant reduction in the incidence of Ac GvHD from 71 to 21% by using a T-cell-depleted stem cell source in the absence of Flu. The incidence of Ac GVH is even lower when using Flu (16%) in both T-cell-depleted and in a minute cohort of non-T-cell-depleted grafts. The incidence of chronic GvHD is 31%.

Mosaicism (the presence of non-FA cells among full-blown FA haematopoietic cells) in the past years has been considered as a negative risk factor for engraftment. These data have been confirmed for those patients transplanted with no Flu-containing regimens but not in those engrafted with Flu-based preparation.¹⁷

Table 2 Results of HSC transplants from alternative (matched unrelated and mismatched related) donors

	<i>Yabe et al.</i> ¹⁸ (27 patients; 24 MUD, 3 MM sib)	<i>De Medeiros et al.</i> ⁹ (47 patients; 15 MUD, 15 MM family non-sib, 17 unrelated CB)	<i>Wagner et al.</i> ¹⁷ (98 patients; all MUD)
Conditioning	CY 40 mg TAI/TBI 300–450 Flu 150–180 mg	CY 33 patients TBI 8 patients FLU 22 patients	CY + TBI/TAI/TLI/96 patients + FLU 46 patients *T-cell depletion 70 patients
Graft failure	4%	49% (8/15 MUD, 5/10 mm family, 10/17 UCB)	21% PMN failure 55% Plt failure
Acute GVHD ≥ 2	11%	47%	29% overall ^b
Chronic GVHD	30%	23%	31%
TRM	4%		47% with Flu, 81% no Flu
Late tumour	NR	NR	NR
Follow-up median (range)	37.1 months (range 7.9–56.3)	8 months (range 6–97)	FLU recipients: 41 months (range 10–69) Non-Flu: 135 months (range 63–163)
Overall actuarial survival rate	96%	38%	53% with Flu 13% no Flu

Abbreviations: MM = mismatched donor; MUD = matched unrelated donor; NR = not reported.

*T-cell-depleted bone marrow cells were infused.

^bIncidence of acute GVHD ≥ 2 divided by conditioning regimen: 70% when no FLU and no T-cell depletion; 21% when no FLU but with T-cell depletion; 16% with FLU and with T-cell depletion (96% of Flu patients received T-cell depletion).

In summary, nowadays Flu must be considered as an essential part of the conditioning regimen in alternative donor transplants for the significantly improved survival, reduced Ac GVH and lowered toxicity. T-cell depletion, which is more widely used by the US transplant centres, turned out to be effective in reducing GvHD. However, it has to be noted that, in Japanese patients¹⁸ who received a non-T-cell-depleted graft, Ac GvHD rate was even lower than that of the Americans¹⁷ who indeed received a T-cell-depleted transplant. Although numbers of patients and ethnicities of the two studies are different, these data seem to suggest that, in the presence of Flu, T-cell depletion may not be very crucial in abating Ac GvHD.

Cord blood is another source of HSCs. At the time of writing, we are aware of 100 unrelated cord blood transplants in FA patients from the Eurocord Registry (data provided by Eliane Gluckman). About one-sixth of them were transplanted with an HLA-identical and the remaining with a non-HLA-identical cord blood donor. The overall survival is close to that of marrow source of cells in the pre-Flu era and seems to be improved by the use of Flu in the conditioning regimen.

Table 2 provides transplantation details and the results of the three largest cohorts of patients engrafted from alternative donors.

Post transplant malignancies

FA patients have *per se* an increased tendency to develop malignancies, primarily AML, MDS and squamous cell carcinomas of the head, neck and oesophagus. HSCT is likely to increase this tendency. Approximately 40% of FA patients develop a malignancy within 15–20 years after HSCT,¹⁹ but indeed head and neck squamous cell carcinomas may occur earlier after transplant at a median of 8.2 years from the graft in patients conditioned with low-dose CY + TAI who had extensive GvHD.¹⁵ Another recent study¹⁶ demonstrated that transplanted FA patients have increased risk and earlier occurrence of head and neck

squamous cell carcinomas compared with non-transplanted FA patients and confirmed the strong association between GvHD and late malignancies. Although transplant results have now importantly improved in terms of quality and duration of engraftment and reduction of toxicity, it looks clear, on the basis of these data, that strategies in FA patients should now aim to minimize GvHD in the view of reducing the risk of late post transplant malignancies. In this respect, Flu-based conditioning regimen and T-cell depletion seem to be promising strategies.

Experimental treatments

Gene therapy programmes were initiated in the 1990s. Probably, no more than 10 patients were treated with this approach. In no case was there long-term haematopoietic reconstitution, the major problem being the low efficiency of transfection of the target cells, which in turn depended on the scarcity of stem cells²⁰ and on the viral vectors. At present, gamma retroviral²¹ and lentiviral vectors²² seem to provide encouraging results in transfecting FA bone marrow cells, whereas a fully convincing strategy capable of expanding the cellular target still seems difficult to find.

A new approach based on the use of agents against pro-inflammatory cytokine TNF- α (Etanercept) is now under evaluation by independent investigators in Italy and USA. The rationale of this strategy is that FA haematopoietic cells display excess apoptosis in response to TNF- α , which acts via increased production of reactive oxygen species, which in turn are harmful to FA marrow cells. Also, in this case, to improve marrow function, it is required that some residual effective haematopoiesis be left.

Algorithm for treatment decision

Soon after diagnosis, the patient has to be placed in a monitoring programme aiming to identify early signs of marrow failure and clonal haematopoiesis as well as that of

head, neck and gastrointestinal cancers. This plan should include physical examination, gastrointestinal endoscopy if a gastrointestinal tract lesion is suspected and yearly marrow examination with cytogenetic analysis. In the case of accelerated progression towards marrow failure/clonal haematopoiesis, investigations should be performed more frequently (for example, monthly or every 2–3 months according to the progression) (Figure 1).

Relatives need to be tested for chromosomal fragility (diepoxybutane or mitomycin C test) to exclude they are hidden FA. The patient can be tested for complementation group and mutation analysis and the study can be extended to relatives. Once identified, heterozygous can be used as HSC donor.

If an HLA-identical non-FA donor is available in the family, then HSCT needs to be performed. As transfusions increase the risk of graft failure,¹⁰ it is better to perform the transplant before the patient becomes at increased risk for transfusions or has bleeding symptoms due to minor traumas, or has actually been transfused. This stage usually corresponds to that of a platelet count between 30 and $40 \times 10^9/l$ and haemoglobin around 9 g/100 ml. To avoid the potentially negative effect of the infections, it is advisable that absolute neutrophil count at transplant be above $0.5 \times 10^9/l$.

In addition to the above-mentioned conditions, transplant is indicated in the case of persistent cytogenetic clone and/or in the case of abnormalities of chromosome 7 (especially monosomy), gain of 3q, isochromosome 1p or other abnormalities of chromosome 1. Morphological changes towards MDS or frank AML are also stringent indications for the transplant. In the case of MDS/AML, if a donor is found, preemptive chemotherapy should not be given to avoid unnecessary toxicity. Indeed, leukaemias in FA patients are very difficult to treat, given the combination of a deficient DNA repair system, a consequent exquisite sensitivity to chemotoxic agents and the lack of marrow reserve. If a donor is not found, then low-intensity chemotherapy can be tried, but long-term remission is rarely obtained.

If after diagnosis an HLA-identical family donor cannot be found, then the research for unrelated donor should be started. If an acceptable donor is found, given the higher TRM of alternative over-matched family donor transplants, it can be accepted to engraft patients at a slightly more advanced stage of marrow failure, but still before open transfusion dependence is established.

Unrelated donor transplant has to be performed also in the case of persistent cytogenetic clone particularly in the case of abnormalities of chromosome 7 (monosomy), gain of chromosome 3q, iso chromosome 1 or other anomalies of chromosome 1. Morphological changes towards MDS or frank AML are also clear indications for alternative donor transplant.

If an unrelated donor cannot be found and marrow failure progresses, androgens in combination with steroids can be used, although not in the long term, with the aim of delaying the depletion of HSCs. Experimental treatment (for example, anti-TNF- α) targeted to slow down stem-cell exhaustion and hopefully to prevent the development of clonal haematopoiesis can be adopted only within the framework of approved experimental trials.

If no unrelated donor can be found, then haploidentical family donor transplant can be considered.

Another potential option is *in vitro* fertilization, pre-implantation genetic diagnosis and embryo selection followed, at the end of pregnancy, by umbilical cord blood collection and subsequent infusion at due time. This procedure has been applied with success in a limited number of patients.^{14,23}

Finally, in the absence of any possibility to find a donor, gene therapy can be considered.

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Conflict of interest

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References

- 1 Faivre L, Guardiola P, Lewis C, Dokal I, Ebell W, Zatterale A *et al.* Association of complementation group and mutation type with clinical outcome in Fanconi anemia. European Fanconi Anemia Research Group. *Blood* 2000; **96**: 4064–4070.
- 2 Levitus M, Rooimans MA, Steltenpool J, Cool NF, Oostra AB, Mathew CG *et al.* Heterogeneity in Fanconi anemia: evidence for 2 new genetic subtypes. *Blood* 2004; **103**: 2498–2503.
- 3 Bagby GC, Alter BP. Fanconi anemia. *Semin Hematol* 2006; **43**: 147–156.
- 4 Dufour C, Corcione A, Svahn J, Haupt R, Poggi V, Beka'ssy AN *et al.* TNF-alpha and IFN-gamma are overexpressed in the bone marrow of Fanconi anemia patients and TNF-alpha suppresses erythropoiesis *in vitro*. *Blood* 2003; **102**: 2053–2059.
- 5 Sejas DP, Rani R, Qiu Y, Zhang X, Fagerlie SR, Nakano H *et al.* Inflammatory reactive oxygen species-mediated hemopoietic suppression in Fanconi-deficient mice. *J Immunol* 2007; **178**: 5277–5287.
- 6 Zhang X, Sejas DP, Qiu Y, Williams DA, Pang Q. Inflammatory ROS promote and cooperate with the Fanconi anemia mutation for hematopoietic senescence. *J Cell Sci* 2007; **120**: 1572–1583.
- 7 Alter BP. Inherited bone marrow failure syndromes. In: Nathan DG, Orkin SH, Ginsburg D, Look AT (eds). *Haematology of Infancy and Childhood*, 6th edn. WB Saunders Company: Philadelphia, PA, 2003, pp 280–365.
- 8 Guardiola P, Pasquini R, Dokal I, Ortega JJ, van Weel-Sipman M, Marsh JC *et al.* Outcome of 69 allogeneic stem cell transplantations for Fanconi anemia using HLA-matched unrelated donors: a study on behalf of the European Group for Blood and Marrow Transplantation. *Blood* 2000; **95**: 422–429.
- 9 de Medeiros CR, Bitencourt MA, Zanis-Neto J, Maluf EC, Carvalho DS, Bonfim CS *et al.* Allogeneic hematopoietic stem cell transplantation from an alternative stem cell source in Fanconi anemia patients: analysis of 47 patients from a single institution. *Braz J Med Biol Res* 2006; **39**: 1297–1304.

- 10 Gluckman E, Auerbach AD, Horowitz MM, Sobocinski KA, Ash RC, Bortin MM *et al.* Bone marrow transplantation for Fanconi anemia. *Blood* 1995; **86**: 2856–2862.
- 11 Zanis-Neto J, Flowers ME, Medeiros CR, Bitencourt MA, Bonfim CM, Setubal DC *et al.* Low-dose cyclophosphamide conditioning for haematopoietic cell transplantation from HLA-matched related donors in patients with Fanconi anaemia. *Br J Haematol* 2005; **130**: 99–106.
- 12 Dufour C, Rondelli R, Locatelli F, Miano M, Di Girolamo G, Bacigalupo A *et al.* Stem cell transplantation from HLA-matched related donor for Fanconi's anaemia: a retrospective review of the multicentric Italian experience on behalf of AIEOP-GITMO. *Br J Haematol* 2001; **112**: 796–805.
- 13 Farzin A, Davies SM, Smith FO, Filipovich A, Hansen M, Auerbach AD *et al.* Matched sibling donor haematopoietic stem cell transplantation in Fanconi anaemia: an update of the Cincinnati Children's experience. *Br J Haematol* 2007; **136**: 633–640.
- 14 Tan PL, Wagner JE, Auerbach AD, Defor TE, Slungaard A, Macmillan ML. Successful engraftment without radiation after fludarabine-based regimen in Fanconi anemia patients undergoing genotypically identical donor hematopoietic cell transplantation. *Pediatr Blood Cancer* 2006; **46**: 630–636.
- 15 Socie G, Devergie A, Girinski T, Piel G, Ribaud P, Esperou H *et al.* Transplantation for Fanconi's anaemia: long-term follow-up of fifty patients transplanted from a sibling donor after low-dose cyclophosphamide and thoraco-abdominal irradiation for conditioning. *Br J Haematol* 1998; **103**: 249–255.
- 16 Rosenberg PS, Socie G, Alter BP, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. *Blood* 2005; **105**: 67–73.
- 17 Wagner JE, Eapen N, Mc Millan ML, Harris RE, Pasquini R, Boulad F *et al.* Unrelated donor bone marrow transplantation for the treatment of Fanconi anemia. *Blood* 2007; **109**: 2256–2262.
- 18 Yabe H, Inoue H, Matsumoto M, Hamanoue S, Koike T, Ishiguro H *et al.* Allogeneic haematopoietic cell transplantation from alternative donors with a conditioning regimen of low-dose irradiation, fludarabine and cyclophosphamide in Fanconi anaemia. *Br J Haematol* 2006; **134**: 208–212.
- 19 Deeg HJ, Socie G, Schoch G, Henry-Amar M, Witherspoon RP, Devergie A *et al.* Malignancies after marrow transplantation for aplastic anemia and Fanconi anemia: a joint Seattle and Paris analysis of results in 700 patients. *Blood* 1996; **87**: 386–392.
- 20 Kelly PF, Radtke S, Kalle C, Balcik B, Bohn K, Mueller R *et al.* Stem cell collection and gene transfer in Fanconi anemia. *Mol Ther* 2007; **15**: 211–219.
- 21 Jacome A, Navarro S, Casado JA, Rio P, Madero L, Estella J *et al.* A simplified approach to improve the efficiency and safety of *ex vivo* hematopoietic gene therapy in Fanconi anemia patients. *Hum Gene Ther* 2006; **17**: 245–250.
- 22 Yamada K, Ramezani A, Hawley RG, Ebell W, Arwert F, Arnold LW *et al.* Phenotype correction of Fanconi anemia group A hematopoietic stem cells using lentiviral vector. *Mol Ther* 2003; **8**: 600–610.
- 23 Grewall SS, Kahn JP, Mc Millan ML, Ramsay NK, Wagner JE. Successful hematopoietic stem cell transplantation for Fanconi anemia from an unaffected HLA-genotype-identical sibling selected using preimplantation genetic diagnosis. *Blood* 2004; **103**: 1147–1151.