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Essential thrombocythaemia in children: is a treatment needed?

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The myeloproliferative disorder, essential thrombocythaemia (ET), is extremely rare in children. In adults, thrombosis is the most common complication whereas a low number of children develop thrombosis and/or haemorrhages. Diagnosis of ET is often difficult, but identifying ET from other causes of thrombocytosis is essential, otherwise therapy may be ineffective as the wrong disease will be treated. Only anecdotal experiences have been published with regard to the treatment of paediatric ET. A watch-and-wait strategy seems appropriate in asymptomatic cases and low-dose aspirin should be used to reduce microvascular disturbances. Anagrelide or IFNs may be considered as first-line, and hydroxyurea as second-line therapy. Anagrelide may become the treatment of choice for ET in children if a lack of leukaemogenic potential is confirmed.

Keywords: aspirin, anagrelide, essential thrombocythaemia, hydroxyurea, IFN-α

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1. Introduction

Essential thrombocythaemia (ET) is a rare haematological disease belonging to the group of Philadelphia-negative myeloproliferative disorders (MPD). ET can be complicated by thrombohaemorrhagic events and may progress to myelodysplasia and/or acute leukaemia (AL), especially in cases where myelotoxic drugs are used for long periods [1].

ET usually affects middle-aged individuals [2], being extremely rare in childhood [3]; only few sporadic cases have been reported in the English medical literature. On the contrary, reactive or secondary thrombocytosis (ST) is a common finding among children [4] but it does not carry any complications [5] nor does it require any treatment by itself. The differential diagnosis between ET and ST is therefore of paramount importance.

In adults, ET is considered a clonal disorder, but non-clonal forms of ET associated with a low thromboembolic risk have recently been identified [6]. A high proportion of familial cases have been documented in paediatric series, whereas familial thrombocythaemia is rare in adult [7]. The diversity of ET in children is also suggested by our own experience [8].

2. Essential thrombocythaemia

2.1 Clinical aspects

ET is considered to be the less common and probably the most benign of all MPD, with an incidence of $1 - 5 \times 10^5$ persons/year [9,10] and a higher frequency in females (2.5:1) [11]. However, the widespread use of automated platelet counters in routine diagnostic haematology is likely to facilitate the recognition of increasing numbers of patients. The median age at diagnosis of ET is usually > 60 years, although ~ 20% of cases are recognised in individuals < 40 years of age [12].

The life expectancy of ET patients seems to be normal in most cases [13]. However, the phenotypic expression of ET is heterogeneous, ranging from an asymptomatic course to life-threatening thromboembolic complications [14]. Even though

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the early reviews on ET emphasised haemorrhage as an essential diagnostic criteria (haemorrhagic thrombocythaemia), the most recent studies suggest that major bleedings are seen only in 5 – 15% of patients who satisfy the accepted criteria for the diagnosis of ET [15]. In contrast, a wide variety of thrombotic manifestations, observed in both large and small vessels, occurs in ET and together, they represent a more common problem than haemorrhage. The dominant risk factors for thrombotic complications in ET are age (> 60 years) and a prior thrombotic event [16].

A relevant clinical feature is represented by the possible evolution of ET in AL or myelodysplastic syndrome (MDS) and in concurrent non-haematological malignancies [17]. Leukaemic transformation is established as part of the natural course of ET in some instances. However, concern persists about the long-term safety of cytotoxic therapy in ET, especially in subjects who receive more than one drug during their lifetime [1]. In fact, it is difficult to distinguish between disease- and treatment-related leukaemic transformation. Thus, age at diagnosis is an important criterion in considering treatment options in ET, particularly for younger patients who may face decades of treatment with agents that are not without adverse events [18].

Therapeutic interventions range from watch-and-wait to cytotoxic modalities. Both antiplatelet agents and myelotoxic agents have a role in the treatment of ET.

2.2 In children

Thrombocytosis in childhood is common, and occurs in 6 – 15% of paediatric patients [4], with no difference in frequency between boys and girls. In patients with ST, an alternative cause of an increased platelet count can be found. In fact, thrombocytosis may be caused by both bacterial and virial infections, tissue damage (due to trauma or surgery), inflammatory diseases (i.e., autoimmune or gastrointestinal diseases), splenectomy, tumours, use of medications (e.g., corticosteroids, vinca-alkaloids and adrenaline) or sideropenic anaemia. However, ET is extremely rare in childhood (annual incidence: 0.09) [19] and it is only anecdotal in infants [8]. A high number of children with ET come from families with other cases of ET (familial thrombocythaemia) [7], confirming that these patients do not have a clonal disease [6]. Moreover, the main clinical and laboratory characteristics of adult and paediatric sporadic ET seem to differ.

In adults, thrombosis is the most common and hazardous complication, occurring in ~ 40% of patients [5]. In contrast, a low number of children with ET develop major thrombotic complications, with haemorrhages only occurring in cases of extreme thrombocytosis [3,8]. In children, ET is not an entirely benign disease [7] and headache is often present.

Diagnosis of ET is based on exclusion of other MPD (*bcr/abl* rearrangement, increase in red blood cell mass, increase of reticuline in bone marrow biopsies), sideropenic anaemia (normal iron standing) and of other causes of reactive thrombocytosis [2], as there are no biological markers of the disease available. Thus, it is possible that one can define ET as different nosological entities, which have common phenotypic expression, but not of common origin.

In children with ET, no alteration of karyotype, spontaneous erythroid colony proliferation, serum erythropoietin and thrombopoietin nor platelet function defect were documented [8]. Moreover, no alteration of thrombopoietin and its receptor genes were observed in seven children with ET [unpublished data]. In contrast, such alterations are sometimes observed in adult ET and in familial thrombocythaemias [20].

Diagnosis of ET is often difficult even in adults and it is extremely hazardous in children. Because of the therapeutic and prognostic difference between ET and other MPD, MDS or reactive thrombocytosis, a clear-cut diagnosis is mandatory, otherwise therapy may be ineffective as the wrong disease would be treated.

3. Treatment strategies and available drugs

Drugs currently used for the treatment of ET include cytoreductive drugs, newer platelet-lowering drugs and antiplatelet agents.

3.1 Cytoreductive drugs

3.1.1 *Hydroxyurea*

At present, the most widely used drug in lowering platelet number is hydroxyurea, a non-alkylating hydroxylated derivative of urea. It inhibits cellular DNA synthesis and promotes cellular death in the S-phase of the cell cycle by inhibiting the enzyme, ribonucleotide reductase [21].

Patients taking hydroxyurea require chronic oral administration and, if the drug dose is decreased or terminated, a rebound increase of the platelet count is observed. Hydroxyurea is generally well-tolerated and < 10% of patients need to suspend the treatment due to adverse events. The major concern of using hydroxyurea is the possible risk of inducing AL [22]. Although a significant increase of secondary malignancy is observed when hydroxyurea is used with other cytotoxic agents [1], it is not clear if hydroxyurea alone can increase such a risk [23,24]. Recently, data from Finazzi [23] suggested that hydroxyurea is efficient and safe when used in young ET patients for long periods of time. The experience of the chronic use of hydroxyurea in children stems from sickle-cell anaemia patients. Adverse events or growth failure have not been reported. However, the development of AL is still an open question [25].

3.1.2 *Pipobroman*

Pipobroman, a piperazine derivative which acts as a metabolite competitor of pyrimidine bases, has been successfully used as first-line therapy in patients with ET [26]. The drug is well-tolerated and has a response rate that is similar to that of hydroxyurea. In addition, pipobroman needs to be continued over time. Experience with pipobroman is limited, compared to that of hydroxyurea, and mostly comes from studies in adults with polycythaemia vera. In these cases, pipobroman is suspected to induce a high incidence of AL (14% at 10 years) [27]. There are no reports on pipobroman treatment in children.

Table 1. Therapeutic options in children with essential thrombocythaemia described in English language literature.

N	Pre-treatment symptoms	Therapeutic options	Outcome	Ref.
1	Bleedings	^{32}P	Acute leukaemia	Ozer *et al.* (1960) [39]
1	Major thromboses	No treatment	Asymptomatic	Spach *et al.* (1963) [40]
1	Minor bleeding	Busulphan	Asymptomatic	Lumley (1971) [41]
1	Asymptomatic	No treatment	Myelofibrosis	Freedman *et al.* (1973) [42]
1	Bruises	Busulphan	Asymptomatic	Sceats & Baitlon (1980) [43]
1	Asymptomatic	No treatment	No follow-up	Barnhart *et al.* (1980) [44]
1	Bleeding	No treatment	Asymptomatic	Linch *et al.* (1982) [45]
3+?	2 Major thromboses 1 ?	1 Aspirin 1 Polychemotherapy	2 ? 1 Deceased	Mitus *et al.* (1990) [46]
1	Headache, bleeding	Anagrelide	Asymptomatic	Chintagumpala *et al.* (1995) [32]
1	Asymptomatic	No treatment	Asymptomatic	Kapoor *et al.* (1996) [47]
1	Headache	Aspirin	Asymptomatic	Yoshida *et al.* (1998) [48]
1	Headache, erythromelalgia	Aspirin, IFN-α Anagrelide	Unchanged Asymptomtic	Hermann *et al.* (1998) [29]
2	2 Asymptomatic	2 No treatment	Asymptomatic	Dror *et al.* (1999) [7]
5	1 Budd–Chiari syndrome 2 Asymptomatic 2 Headaches	2 No treatment 1 Warfarin 1 Aspirin 1 IFN	5 Asymptomatic	Randi *et al.* (2000) [8]
9	3 Asymptomatic 3 Headaches 2 Minor bleedings 1 Inferior cava vein thrombosis	3 No treatment 5 Hydroxyurea 1 Busulphan	1 Myelofibrosis 8 Asymptomatic	Yang & Qian (2000) [49]
1	Asymptomatic	Aspirin	Asymptomatic	Chan *et al.* (2000) [50]
1*	Asymptomatic	Aspirin	Asymptomatic	Okada *et al.* (2000) [51]
Grand total				
32+?	12 Asymptomatic 8 Headaches 6 Bleedings 1 ? 5 Major thromboses	12 No treatment 1 Warfarin 5 Aspirin 2 IFN (1+ aspirin) 5 Hydroxyurea 3 Busulphan 1 ^{32}P 2 Anagrelide (in 1 after IFN-α) 1 Polychemotherapy	24 Asymptomatic 2 Myelofibrosis 1 Acute leukaemia 1 Deceased 4 ?	

*XYY syndrome.

N: Number of cases; ^{32}P: Radioactive phosphorus.

3.2 Newer platelet-lowering drugs

3.2.1 Interferon-α

IFN-α is not considered a new drug, as it has been used in the treatment of ET for > 15 years. IFN-α is a cytokine with both immunomodulatory and myelosuppressive effects. Approximately 70 – 80% of patients treated obtain a complete remission with an average dose of 3 mU/day. The most significant advantage of IFN-α is that it is not mutagenic, although it does have frequent intolerable side effects and is extremely expensive. Moreover, it seems that the effect decays rapidly after suspension, as has been our experience in a 9-year-old girl [8]. Recently, some data have suggested that pegylated-IFN is superior to unmodified-IFN in terms of adverse event profile and efficacy [28]. Its use should also limit the discomfort of chronic subcutaneous administration. So far, two children have been treated with IFN [8,29].

3.2.2 Anagrelide

Anagrelide is an oral imidazoquinazoline agent with selective thrombocytopenic effects [30], sparing the other marrow cell lineages. Anagrelide reduces both megakaryocyte mass and ploidy and decreases the platelet count and the turnover rate. It is considered a reasonable component of the therapy in younger patients with ET even though it is approved by the

US FDA only and not from the European Agency for the Evaluation of Medicinal Products (EMEA). The most common side effects of anagrelide are headache, fluid retention, hypotension, tachycardia, arrhythmias, diarrhoea, nausea and abdominal pain, which usually develop within 15 days after the beginning of therapy and resolve within 2 weeks of continued therapy. Anagrelide is considered to be tolerable long-term. Mild-to-moderate anaemia occurs in 25% of ET patients after ~ 2 years of treatment [31]. No leukaemic evolution has actually been reported in anagrelide-treated ET patients. Two paediatric cases have been reported that suggest anagrelide may also be beneficial in children [29,32].

3.3 Antiplatelet drugs

Low-dose aspirin is widely used in patients with ET who are prone to both ischaemic microvascular symptoms and major thrombosis, mainly of the arterial system [33]. However, although the use of aspirin is well-established in the treatment of microvascular disturbances [34] and it is considered useful in preventing major thrombotic complications in patients with associated thrombotic risk factors, it is contraindicated in patients with a history of bleeding, a platelet count of $> 1500 \times 10^9$/l, or acquired von Willebrand's disease [35]. It is noteworthy that aspirin is commonly used in the paediatric cases in the literature to prevent thrombotic complications.

3.4 Cost-effectiveness in the treatment of essential thrombocythaemia

In ET, the factors that influence the choice of drug out of those available are efficacy, safety and cost. In almost all cases, the efficacy and safety data of these drugs are derived from Phase II studies, as no Phase III studies comparing the different drugs are currently available. The individual cost for each available drug has been recently evaluated by Griesshamer [36]. In comparison with hydroxyurea, the newer drugs (anagrelide and pegylated-IFN) seem to have similar efficacy regarding the reduction of platelet count, but it is not clear whether they are as effective in preventing thromboembolic complications such as hydroxyurea [37]. Phase III trials are strongly needed to clarify this.

4. Treatment experience in children with essential thrombocythaemia

Only anecdotal experiences have been published regarding the treatment of paediatric ET (Table 1). Most patients with ET did not receive any drugs. Information may be taken from the treatment used in young patients [31]. However, if therapeutic interventions in adults with ET have been described as a 'compromise between accepting the risk of potentially serious drug toxicity and the necessity of preventing thrombohaemorrhagic complication' [38], this is more likely in children. The treatment of asymptomatic or low-risk adult patients remains problematic and in patients < 18 years of age, the incidence of complications and consequently, the indications for treatment, are less certain [7]. The platelet count below which the risk of complications is negligible is unknown, nor has the benefit of lowering the platelet count of $< 600 \times 10^9$/l been established, especially in younger patients. Furthermore, concern exists about the leukaemogenic potential of drugs for lowering platelet number; however, it is noteworthy that none of the paediatric patients treated with hydroxyurea underwent malignant transformation. Anagrelide controls extreme thrombocytosis and the only two available cases [29,32] treated with such a drug suggest no carcinogenetic effects.

5. Expert opinion and conclusion

The rare occurrence of thrombotic complications in children with sporadic ET seems to classify these cases as low-risk ET. However, the individual clinical course is variable with some patients facing life-threatening complications. Due to the expected long survival of all patients with ET, in children it is imperative that the treatment is both well-tolerated and efficacious long-term.

For asymptomatic and low-risk patients, a watch-and-wait strategy is appropriate and cost-effective. Low-dose aspirin should be used to reduce microvascular disturbances in the patients complaining of headache. However, the efficacy of aspirin alone in preventing major thrombotic complications has not yet been definitely established. Cytoreductive treatment may be indicated only in the rare cases of children with previous major thrombotic complications but there is no clear preference out of the various available drugs. At present, it is our view that the use of ^{32}P, busulphan or other alkylating agents be avoided because of the great risk of leukaemia in children who face many decades of treatment. We suggest the use of anagrelide or IFNs as first-line and hydroxyurea as second-line treatment. However, presently, no definitive conclusions can be drawn and only prospective co-operative trials may help in clarifying such a problem. Anagrelide may become the treatment of choice in children with ET if a lack of leukaemogenic potential is confirmed.

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