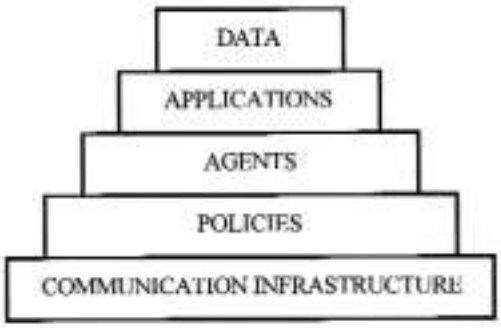

Figure 1. The five-tier RIMM organizational model.

ment of physicians. Other early evidence produced by the RIMM project was a hint about MMM epidemiology. The 72-year median age of the collected patients was older than the 54-62 year median age reported in literature[1] and 7.6 years higher than that which we had previously observed in an Italian multicenter study.[3] The older age of the population was attributable to the 60% of cases who received a diagnosis in Internal Medicine wards whose median age was 75 years compared to the 65 years of patients cared for in the Hematology Units (Mann-Whitney U test: U = 1228, p = 0.004) (Table 1). This speaks in favor of a referral selection bias in multicenter studies. As to the quality of care, diagnostic guidelines proved to be a useful tool for standardization and education. According to the Italian Consensus Conference criteria for diagnosis,[4] a MMM patient should have the Philadelphia chromosome or the BCR-ABL molecular rearrangement searched for and found negative, and should have typical morphologic features on a peripheral blood smear, such as red cells with teardrop shape, immature myeloid cells and erythroblasts. In 55 cases, the diagnosis was reached by examination of blood samples or slides sent from the participating centers to the co-ordinating center.

Table 1. Data from the population-based Registry of Myelofibrosis with myeloid metaplasia (RIMM).

	Number (%)	*Age (median and range in years)*
Collected cases	168	72 (42-96)
Males	115 (68%)	72 (42-96)
Referred to RIMM from Internal Medicine Centers	104 (62%)	75 (51-96)
Referred to RIMM from Hematology Centers	64 (38%)	65 (42-90)

One requisite of the Registry was an exhaustive nationwide collection of cases. Even after a third invitation, we have not been able to involve all clinical Centers that may occasionally observe a case of MMM in Italy. We cannot, therefore, assess how many MMM patients are not reported. Cross-checking reporting from clinical wards with reporting from pathologists showed a 21% referral discordance that was almost eliminated after active co-ordinating center intervention. Nevertheless, the incidence of the disease, as emerging from this first year of activity of the Registry, is far lower than expected. Continuation of the study will give us information useful for widening the network of hospitals and for reassessing the reporting criteria.

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Advances in iron chelating therapy

Iron overload in chronically transfused patients is a serious complication giving rise to damage in organs such as the heart, liver, and endocrine system and leads to a shortened life-expectancy.[1,2] The introduction of the iron chelating agent deferoxamine, which prevents oxidative damage due to iron overload, has dramatically reduced the mortality and improved the quality of life in regularly transfused patients over the past twenty years.[3-11] However this therapy requires a high patient compliance since deferoxamine must be administered chronically by subcutaneous continuous infusion.[12,13] There has, therefore, been a search for a more effective and easier way to administer iron chelating

agents.[14,15] In this report we present the main new developments in iron chelating therapy by analyzing both new techniques of administering commonly used drugs and new molecules.

Deferoxamine

Deferoxamine is a natural siderophore, first isolated from *Streptomyces pylosus*, capable of complexing with iron and promoting fecal and urinary excretion of this latter.[14] It is a trihydroxamic acid with poor intestinal absorption which is rapidly metabolized in plasma (half-life of only 5-10 minutes); for this reason continuous parenteral infusion is the route of administration necessary for optimal clinical effect.[3-6] This drug was first used intramuscularly in the early sixties and successfully slowed down iron accumulation and stopped hepatic fibrosis in transfusion-dependent thalassemic patients.[3] However it was not until the early seventies that modern iron chelating therapy began thanks to the battery-operated portable pumps which enabled deferoxamine to be administered by continuous subcutaneous infusion over 12 hours.[5] This method, which is equivalent in terms of urinary iron excretion to continuous intravenous infusion, has been the most widely used over the past 20 years and induces a negative iron balance in regularly transfused patients.[9,16] The very demanding nature of this therapy, from the patient's point of view, has led researchers to investigate both new techniques for administration (twice daily subcutaneous bolus injection) and deferoxamine derivatives (HES-deferoxamine, deferoxamine-depot) which can be infused over shorter periods.[14]

Twice daily subcutaneous bolus injections

Recent studies[17-22] on thalassemic and non-thalassemic patients have reported that urinary iron excretion after twice daily subcutaneous bolus injections is similar to urinary iron excretion after continuous subcutaneous infusion over 12 hours with portable pumps. These bolus injections are well tolerated locally and are associated with high patient compliance. A preliminary study[23] has emphasized the efficacy of this new technique which can be compared to continuous subcutaneous infusion when it comes to reducing non-transferrin-bound iron, the main culprit of most iron-induced oxidative damage.

We recently assessed the long-term efficacy of twice daily subcutaneous bolus injections of deferoxamine by analyzing ferritinemia in 27 transfusion-dependent adult patients with oncohematologic disorders and mild-moderate iron overload. After a 20-month follow-up, subcutaneous bolus injections of deferoxamine were well tolerated, and were as safe and as effective as continuous subcutaneous infusion in controlling iron burden.[24] However these are only preliminary results and before this method can be considered as a valid alternative to continuous subcutaneous infusion it also needs to be evaluated in patients with higher iron overload who require larger doses of deferoxamine, such as thalassemic patients.

Hydroxyethyl starch deferoxamine

This high molecular weight chelator has been obtained by binding hydroxyethyl starch polymer (HES) to deferoxamine.[14] This molecule has the same affinity for iron as deferoxamine but its plasma half-life is 10-30 times longer.[25] Intravenous HES-deferoxamine infusion over 4 hours at 80 mg/kg induces urinary iron excretion equal to that produced by 3 days of subcutaneous deferoxamine treatment, with no side effects.[26] However a limited amount of data about its efficacy and tolerability is available and further studies are needed before this drug can be used clinically.

Deferoxamine-depot

Deferoxamine-depot (ICL749B) is a new salt derived from the modification of deferoxamine which is then suspended in a lipid carrier for slow release. This formulation, which can be administered by subcutaneous injection, is active for about 30 hours thus reducing the volume and administration time of the chelating drug. Although preliminary studies had shown the tolerability and efficacy of this formulation of deferoxamine,[26] a recent study of 112 thalassemic patients to assess tolerability, pharmacokinetics and urinary iron excretion has concluded that the depot formulation is less effective and less well tolerated than continuous subcutaneous infusion of standard deferoxamine.[27]

Orally active iron chelators

The creation of an orally active iron chelator which frees the patients from parenteral infusion is the main aim of the research in this field. Various oral iron chelating agents are under study but the most interesting and widely experimented is deferiprone (L1; 1,2 dimethyl 1-3-hydroxypiridin-4-one).[28,29] This drug was synthesized in 1982 but has been studied systematically only recently. When administered at 75-100 mg/kg/day it induces a negative iron balance in regularly transfused patients.[30-33] The most frequent side-effects are arthropathy and gastrointestinal disturbances. The most severe complication, which disappears when therapy is suspended, is the onset of neutropenia/agranulocytosis.[29] Although this complication is rare it is advisable to check white

blood cell count weekly during treatment with deferiprone. The progression of hepatic fibrosis during treatment with deferiprone reported by a few authors,[34,35] has not been confirmed by further studies.[30-33,36,37] The long-term efficacy of deferiprone is difficult to assess due to short follow-up studies. A recent meta-analysis[38] of the main deferiprone clinical trials since 1989 concluded that at least 75 mg/kg/day of this drug is clinically effective in inducing a negative iron balance and reducing the body iron burden in iron overloaded patients. A recent Italian study[32] of 114 thalassemic patients compared the clinical efficacy of deferiprone (75 mg/kg/day) with the conventional therapy of deferoxamine (50 mg/kg/day subcutaneously) by analyzing ferritinemia, hepatic fibrosis and liver iron concentration at the start and the end of the follow-up period. After a year's treatment there was no statistically significant difference between the 2 groups of patients. However further studies on larger patient populations are needed to verify the drug's long-term safety, efficacy and impact on iron-related cardiac complications and survival.[39,40] In August 1999 the *European Agency for the Evaluation of Medical Products (EMEA)* authorized the sale of this drug for patients with iron overload for whom traditional therapy with deferoxamine is contraindicated or has caused severe toxic effects. This drug has been on sale in Italy from February 2000.

Conclusions

Over the past few years some alternative drugs or alternative methods of administering known drugs have been developed to increase the compliance of transfusion-dependent patients to therapy, this compliance being somewhat poor to traditional continuous subcutaneous infusions of deferoxamine. From among such alternative drugs, deferiprone appears to be the most interesting. However, due to the paucity of data on the long-term efficacy and safety of this drug, we suggest that, at present, the traditional therapy with deferoxamine must be considered the treatment of first choice for iron overloaded patients.

Moreover, if studies on thalassemic patients confirm the efficacy of twice daily subcutaneous bolus injections, these may be considered a valid alternative to traditional continuous subcutaneous infusion therapy, especially in patients with poor compliance.

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Antitumor vaccination

Several studies are currently evaluating the efficacy and safety of tumor-specific vaccination strategies in cancer patients. In this issue of Haematologica, Bocchia et al report an extensive review on this exciting subject. Other papers on this topic have been published in recent years.[1-8]

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Stem Cell Disorders

Relevance of bone marrow features in the differential diagnosis between essential thrombocythemia and early stage idiopathic myelofibrosis

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ABSTRACT

Background and Objectives. **Diagnosis of essential thrombocythemia (ET) remains a challenging problem and has been predominantly established by exclusion of other thrombocythemic disorders. In this context the updated diagnostic criteria of the Polycythemia Vera Study Group (PVSG) are generally accepted, although histopathologic features of the bone marrow were only marginally considered.**

Design and Methods. **A retrospective evaluation was performed of 168 patients presenting with ET in accordance with the criteria of the PVSG. Analysis was focused on the discriminating impact of bone marrow morphology.**

Results. **Histopathology revealed that our cohort of patients could be divided into three distinct groups (true ET, questionable ET and false ET). These groups were characterized by certain diagnostic constellations of clinical data on admission. True ET was found in 53 patients presenting with no or a borderline splenomegaly and no relevant anemia or leuko-erythroblastic blood picture. The other patients showed clinical signs and symptoms which were more compatible with initial-prefibrotic (52 patients) or early (68 patients) idiopathic-primary myelofibrosis (IMF) with severe thrombocythemia. In true ET no significant hypercellularity of the bone marrow including myeloid precursors or an increase in reticulin fibers was detectable. Most prominent were changes of megakaryopoiesis which revealed large to giant-sized cells lacking a definite maturation defect. Their appearance in true ET contrasted with the clusters of abnormally differentiated, often bizarre elements of this lineage in patients with initial and early IMF (questionable or false ET). Calculation of survival disclosed a relevant disparity with a non-significant loss in life expectancy of 10.9% in true ET compared to 29.6% in questionable and 51.3% in false ET. Follow-up studies and repeated bone marrow biopsies revealed no transition into myelofibrosis in true ET, whereas this did occur in 22 of 27 patients with questionable and false ET. In the latter cohort bone marrow changes were accompanied by increasing anemia, splenomegaly, tear-drop poikilocytosis and reduction of the platelet count consistent with IMF.**

Interpretation and Conclusions. **A detailed evaluation of bone marrow features, in particular megakaryopoiesis is recommended to establish positive criteria for the diagnosis of ET and thus to accomplish a significant improvement of the PVSG postulates. In this context ongoing clinical trials on ET must regard pretreatment bone marrow biopsies as a major clue to diagnosis.**

Key words: essential thrombocythemia, early myelofibrosis, diagnostic criteria, megakaryopoiesis, survival, bone marrow biopsies

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Essential (primary, hemorrhagic) thrombocythemia (ET) is a relatively rare chronic myeloproliferative disorder (MPD) characterized by a sustained elevation of the platelet count and an increased incidence of thromboembolic or hemorrhagic episodes.[1-5] Although most patients are asymptomatic at diagnosis[3,5] and the overall survival is comparable to that of the general population,[5-7] controversy and discussion still persist regarding stringent diagnostic criteria. There have been many years of arguments about realiable guidelines to establish ET as well as great difficulties in designing randomized therapeutic trials.[4,8] In the context of relatively ill-defined parameters within the spectrum of MPDs, ET remains a diagnosis of exclusion.[1,2,5,8,9] This fact has been appreciated by the *Polycythemia Vera Study Group* (PVSG) and finally emphasized by their updated criteria.[10] On the other hand, regarding these widely accepted postulates which have been generally used in clinical studies,[11-21] some authors have recently called attention to an obvious shortcoming which may impair diagnostic accuracy. This point includes a more scrutinized definition of morphologic parameters and thus attempts have been made to revise the original criteria by