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Editorial and Views

The Italian Registry of Myelofibrosis is one year old

On the 1st of June 2000, the *Italian Registry of Myelofibrosis with Myeloid Metaplasia* (RIMM) completed its first year. Myelofibrosis with myeloid metaplasia (MMM) is a rare chronic myeloproliferative disorder that mainly affects patients in mature or old age and reduces their life expectancy to 3.5-5.5 years.[1] The RIMM was promoted as a permanent organization to maintain a data file of patients with MMM collected throughout the whole of Italy. The project was conceived as a challenging way to overcome cultural and operational barriers to clinical and research medicine dealing with a rare disease. According to the estimated incidence of the disease,[2] we expect roughly 322 new cases each year in Italy. The traditional organization of health care and research, in Italy as in other countries, makes this an orphan disease and does not allow a sufficient number of cases to be collected quickly enough to perform controlled clinical trials. The result is that among Medline's 397 citations on MMM in the last 10 years no controlled clinical trials appear, making evidence-based medicine far from being applicable in this disease. The main goal of the Registry was to move from a collection of incident cases to a prospectively followed country-wide population of patients. With this information at hand, the epidemiology of the disease, its natural history, its outcome and process of care, as well as the clinical and biological research hypotheses could become specific objectives with possibilities of being pursued. The second goal of the RIMM project was to guarantee quality and continuity of care through diffusion of guidelines and co-operation between centers.

From January to June 1999 the project was presented to all the Italian Institutions of Internal Medicine and Hematology. Pathology Institutions were also asked to participate to guarantee complete patient referrals via bone marrow biopsy reporting. Three hundred and eighty-four (37%) of the Units of Internal Medicine, 95 (88%) of the Hematology and 195 (74%) of the Pathology ones responded and agreed to participate in the project. The participating doctors, together with the co-ordinating center team and 5 representatives of the GIMMC (*Gruppo Italiano Malattie Mieloproliferative Croniche*) Scientific Committee, formed the "agents" tier of the five-tier model of the Registry (Figure 1). The collaborative policies (ownership, liability, intellectual property, confidentiality, security) and the communication infrastructure (Internet-based applications, prepaid transport and mailing services) were two other tiers of the organizational model. Overall expenditure for Registry implementation was Italian Liras 140,000,000 (US$ 70,000) and was caused by personnel (57%), mail (17%), printing office (10%), telephone (8%) and informatics support (8%).

From the 1st June 1999, participating centers sent, by mail or by modem, a detailed predesigned report of each observed patient for whom a definite or presumptive diagnosis of MMM had been made. The report requested data on the epidemiology of the patient, on the history, presentation and follow-up of the disease. Moreover, a detailed report of diagnostic tools and therapies used was requested for the data on the process of care, as well as medical resources utilized (days of hospitalization, number of outpatient visits, intensity of referrals for second opinions). The data (the fourth tier of the model) were analyzed at the co-ordinating center and any further request needed to fulfil the guideline-based diagnostic criteria[2] or useful for specific applications implemented in the Registry (the fifth tier), were reported back to the doctors.

What are the results of the RIMM project so far? Active center networking, aimed at health care and research for a rare disease, has been proven feasible. As of the 1st June 2000, 168 cases have been referred to the Registry. One hundred and sixty-one met the criteria for a diagnosis of MMM; in 7 cases an alternative diagnosis was reached (myelodysplasia with bone marrow fibrosis in three, polycythemia vera in two, essential thrombocythemia and paroxysmal nocturnal hemoglobinuria in one). These results were the fruit of intense co-operative work: the co-ordinating center had a mean of 5 contacts every day with participants, either as telephone calls, faxes or e-mails, or as mailed material. Maintaining the Registry for one year cost approximately US$ 30,000. The interest shown by the physicians was high and new centers continue to ask to join the Registry. Proper presentation of the project during specific meetings and continuous training of the doctors participating in the project about the rules of the Registry were crucial elements in the involve-

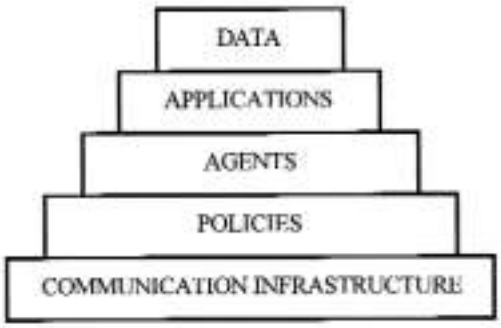

Figure 1. The five-tier RIMM organizational model.

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.

Giovanni Barosi, Monia Marchetti, Cristina Azzan, for the Italian Registry of Myelofibrosis with Myeloid Metaplasia

Laboratory of Medical Informatics, IRCCS Policlinico S. Matteo, Pavia, Italy.
E-mail: barosig@smatteo.pv.it

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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