Primary cutaneous lymphoma: the witness of multidisciplinarity

Primary cutaneous lymphoma (CL), the second most frequent type of extranodal non-Hodgkin's lymphoma (NHL), accounts for approximately one third of all cases of NHL. This is a very simple reason for having an issue of Haematologica specifically focused on this topic. Although most of the literature and clinical experience about CL come from dermatology, the history of the last 20 years clearly shows the critical importance of the close integration among scientists from different disciplines: dermatology, pathology, hematology, oncology, radiotherapy, immunology, and molecular biology. This is increasingly recognized as the only way to progress in an effective and balanced fashion. The continuous efforts of the Cutaneous Lymphoma Task Force of the European Organization for the Research and Treatment of Cancer (EORTC-CLTF) bear witness to the crucial importance of multidisciplinary groups. In 1997, this Task Force produced the clinico-pathological classification which is currently the most effective and powerful reference for diagnosis, management, and treatment of CL. Right at the moment dedicated people from the EORTC-CLTF are finalizing the dream of producing a WHO/EORTC consensus classification of CL, with the goal of having CL patients correctly diagnosed, properly managed and effectively treated. The EORTC-CLTF includes clinicians and scientists from various European countries, some of which have well established and active national groups, such as the Dutch group (very strong, and operating for almost 20 years), the French, British, German-Austrian, Spain and the Italian (Gruppo Italiano Linfomi Cutanei, GILC, founded in 1998) groups. One of the goals of the national groups is to develop consensus guidelines for diagnosis, management and treatment of CL, and to spread them to practicing physicians. This respectable goal is also one of the priorities of international organizations such as the International Society for Cutaneous Lymphomas (ISCL), in which most of the people of the EORTC-CLTF work in close collaboration with clinicians and scientists from every part of the world in a truly intercontinental effort. I have no hesitation in recounting that being one of the active supporters of both the EORTC-CLTF and ISCL, together with other Italian and non-Italian friends, was — and is — a great privilege for me.

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References

Cytoreductive therapy for patients with essential thrombocytemia at high risk of thromboembolic complications. The difficult choice of the optimal drug

Essential thrombocytemia is the chronic myeloproliferative disorder with the most favorable outcome. In fact, in large cohort studies patients with essential thrombocytemia showed equal or only slightly shorter survival than an age- and sex-matched healthy population. In a very recent study, we have assessed life expectancy and prognostic factors for survival in 831 consecutive patients with polycythemia vera or essential thrombocytemia. Life expectancy of patients with polycythemia vera (especially if younger than 50 years) was reduced compared with that of the general population, whereas life expectancy of patients with essential thrombocytemia was not affected significantly by the disease, reflecting a more indolent nature of the proliferation.

The major problem in essential thrombocytemia is thromboembolic complications. According to the practice guidelines from the Italian Society of Hematology on the therapy of essential thrombocytemia, candidates for cytoreductive or platelet-lowering therapy include:
- patients who are above the age of 60 years, have a history of major thrombosis or major bleeding, or have a platelet count over 1500x10^9/L;
- patients who are between the ages of 40 to 60 years, have a platelet count greater than 1000x 10^9/L and a cardiovascular risk factor (i.e. smoking, arterial hypertension, hypercholesterolemia or diabetes mellitus) or familial thrombophilia;
- patients younger than 40 years of age with a comorbid condition that greatly increases their thrombotic risk (homocystinuria, familial dominant hypercholesterolemia);
- patients who suffer from severe microcirculatory symptoms despite anti-platelet therapy.

The drugs currently available for platelet-lowering therapy include busulfan, pipobroman, hydroxyurea, interferon-α and anagrelide. Nowadays busulfan is rarely employed due to its established mutagenic effects.
We evaluated the efficacy and safety of pipobroman in the long-term control of essential thrombocythemia in 33 consecutive young patients at high risk of thrombosis followed for a median of 15.8 years. Pipobroman proved to be very effective in preventing thrombosis, and there was only one case of acute leukemia, which might be part of the intrinsic risk found in patients with essential thrombocythemia irrespective of treatment.

Most patients who need cytoreductive therapy are currently receiving hydroxyurea. In a long-term study on patients with sickle cell anemia, Steinberg and co-workers found no evidence of increased propensity to evolution into acute leukemia. However, the leukemogenicity of hydroxyurea in chronic myeloproliferative disorders is still controversial. Tettieri concluded that published reports on the association of hydroxyurea and acute leukemia are inconsistent, and that the strength of the association is very small. We found a 15-year cumulative risk of acute leukemia of 2% in patients with essential thrombocythemia receiving pipobroman or hydroxyurea, clearly indicating that the leukemogenic potential of these drugs is definitely low. This also shows that it is very difficult to design a study to compare the leukemogenic potential of different cytoreductive agents, and also to dissect the intrinsic risk of chronic myeloproliferative disorders from any additive effect of cytoreductive drugs.

Interferon-α does not appear very suitable for long-term treatment of Philadelphia-negative chronic myeloproliferative disorders due to its several adverse effects, which result in poor quality of life and treatment withdrawal in a substantial proportion of patients.

Since a few years ago, anagrelide has been employed as a cytoreductive drug in the treatment of essential thrombocythemia. This drug is unlikely to have any leukemogenic effect, but its ability to prevent thrombosis in young patients is uncertain. In this issue of Haematologica, Mazzucconi et al. report the results of a long-term study of patients treated with anagrelide to control thrombocytosis. According to their findings, anagrelide appears suitable for long-term control of thrombocytosis in patients with essential thrombocythemia. However, reducing the platelet count is a surrogate end-point, the primary hard end-point being prevention of thrombosis. Two out of 39 patients treated by Mazzucconi et al. had major thrombotic events. The authors conclude that anagrelide may be used in patients younger than 60 years, with the exclusion of women of child-bearing potential and in of subjects aged 40-60 years with a history of major thrombotic events.

Birgegard and co-workers recently reported in this journal the adverse effects and benefits of two years of anagrelide treatment for thrombocythemia in chronic myeloproliferative disorders. In their long-term prospective study of the feasibility and toxicity of anagrelide treatment, side effects and toxic discontinuation rates were higher than in the Italian study. In this latter, one patient had a myocardiitis, whose nature could not be clearly established, but cardiac muscle fibers recovered after discontinuation of anagrelide. Mazzucconi et al. discuss this side effect concluding that anagrelide should not be administered to patients with cardiac disorders, and that a careful approach to treated patients should include monitoring of heart function before and during treatment. Interestingly, in this month’s issue of the journal, Jurgens et al. report cases of a potentially reversible drug-induced cardiomyopathy in anagrelide-treated patients with either polycythemia vera or essential thrombocythemia. The mechanism of action may involve the drug’s known cardiovascular effects including positive inotropism, vasodilatation, and tachyarrhythmia. Anagrelide therapy was temporarily associated with this particular complication in 6 patients, all of whom experienced symptomatic and/or objective improvement after drug discontinuation. This emphasizes the need for closely monitoring of heart function in patients receiving anagrelide. It should also be noted that a clinical trial on the combined use of hydroxyurea plus aspirin or anagrelide plus aspirin in high-risk patients with essential thrombocythemia (PT-1 trial) was prematurely closed towards the end of 2003 because of an excess of adverse events in the anagrelide arm. A German study comparing hydroxyurea and anagrelide is ongoing.

In conclusion, we believe that the available evidence still supports the use of hydroxyurea or pipobroman as an effective and safe cytoreductive treatment for prevention of thromboembolic complications in high-risk patients with essential thrombocythemia.

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Risk of deep vein thrombosis: interaction between oral contraceptives and high factor VIII levels

Oral contraceptive use is associated with a significant increase in the risk of venous thromboembolism. It has been previously reported that some thrombophilic alterations such as factor V Leiden and G20210A prothrombin mutation display a synergistic interaction with oral contraceptive use. Heterozygous carriers of these mutations who use oral contraceptives have a 20- to 40-fold higher risk of thrombosis than non-users who have a normal genotype.

High levels of factor VIII are another common risk factor for venous thromboembolism. In this issue, Legnani and co-workers show that the risk of venous thromboembolism due to oral contraceptives is increased further in women with elevated levels of factor VIII, and that the raised levels of the coagulation factor and oral contraceptive use likely have a synergistic effect. A few papers on this topic have previously appeared in the journal. In addition, a Continuing Medical Education quiz in this issue deals with the interaction between oral contraceptives and high factor VIII levels, and the risk of deep vein thrombosis in women (http://cme.haematologica.org/).

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