How Haematologica serves the scientific community

Taking on the job of Editor-in-Chief I want to clarify how Haematologica serves the scientific community by briefly examining a few key issues.

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Peer-review: «Crude and understudied, but indispensable»

The readers interested in learning more about peer review are referred to the online proceedings of the Fourth International Congress on Peer Review in Biomedical Publication, September 14-16, 2001, or more generally to the web site of the World Association of Medical Editors (WAME), which I am proud to belong to.

Our opinion about peer review is summarized by the title of the article that Kassirer and Campion wrote in 1994: Peer review. Crude and understudied, but indispensable.

How does Haematologica choose reviewers? We have our own data base that is continually updated. Our preferred approach, however, involves a MedLine® search using 2-3 key words in order to focus on the specific topic: in this way we pick out scientists who have direct experience in the field. The Associate Editor responsible for the peer-review process should have a broader view of matter. He or she not necessarily must belong to our board: since our true editorial board is the scientific community, we often ask somebody else to act as an Associate Editor.

The fundamental questions to which the reviewers should provide answers are if the work is methodologically correct, and if the paper under examination adds something to what is already known on the topic. Although some confirmatory papers are worth publishing, the advancement of science by definition requires new observations. Starting this issue, we publish the main outcomes of the peer-review process of research articles. This is a step forward in improving the peer-review, although a lot of work remains to be done. For instance, our colleagues at BioMed Central operate a system of open peer review for submitted papers. This means that reviewers' signed reports are passed onto the authors and, if the paper is accepted for publication, signed reports are posted on the BioMed Central website as part of the pre-publication history. An informal opinion poll within a sample of our reviewers has indicated that most of them would not be willing to unmask their reports at present (M. Cazzola, unpublished observation, 2001).

A difficult issue regards the quick rejection policy. Each paper submitted to Haematologica is read inhouse initially. If the editors judge that a manuscript contains no new information, or it doesn’t adhere to the relevant standards for reporting, or is poorly written, they will proceed to a quick rejection.

The print journal (Haematologica, ISSN 0390-6078) and its online version as tools for circulating research papers across all areas of experimental and clinical hematology

The coming of electronic journals has created an complex scenario in scientific publishing. Most journals now have two editions with different ISSN (International Standard Serial Number); the print one, and the purely electronic one. The impact fac-
We will consider the Haematologica’s print edition exclusively as a journal of research papers and highly focused review articles. Therefore, the print journal will mainly report original papers across all areas of experimental and clinical hematology. To be considered as original papers, clinical studies should be prospective; retrospective studies cannot be accepted as original papers unless they provide observations of major relevance for clinical practice.

Review articles are welcome provided that they carry new information to the reader and not simply a general, dull overview. We favor Decision Making and Problem Solving papers, which may include: a) meta-analyses; b) consensus statements, guidelines, recommendations or position papers by scientific societies or groups; c) problem solving papers. Updates on molecular basis of disease and on recent advances in molecular biology are very welcome provided that they also included information (at least potential implications) for clinical practice. Reviews may also concern borderline fields, considering that Haematologica’s view of hematology is broad, and we should be considered a journal of hematologic medicine.

Scientific letters are studies that can be reported in shortened way as compared to original papers.

The purely online journal (Haematologica on Internet, ISSN 1592-8721) as an educational tool

Because we have no space constraints online, we will publish several items deemed by peer review to be scientifically sound and useful as educational papers. These will include: a) case reports; b) irreplaceable images (published in the print edition until 2001); c) educational material from scientific meetings; d) meeting abstracts; letters to the Editor.

Bridging the information gap between North and South, or West and East of the world

Haematologica is absolutely willing to help scientists from countries with limited economical resources. This issue is very important to many of us, directly involved in medical and scientific cooperation with the South or the East of the world. Our policy in this field has been explained by Masera in a recent editorial, but I want to reaffirm here that Haematologica wants to play a role in solving the global information poverty.

Concluding remarks

Having clarified how Haematologica serves the scientific community, we now hope to receive feedback from authors and readers. Any criticism will be carefully evaluated by the editors, and a forum online will be open if required. We are flexible and prepared to changes if the incoming suggestions will be convincing, since our major aim is the benefit of scientific progress and education.

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Autotrasplantation for chronic myeloid leukemia: is it useful?

Autologous stem cell transplantation (ASCT) was first attempted for patients with chronic myeloid leukemia (CML) in transformation in order to restore a second chronic phase. In 1978, Buckner et al. used bone marrow harvested during the chronic phase to rescue hematopoiesis after a supralethal myeloablative conditioning regimen including total body irradiation (TBI). Subsequently, Goldman et al. reported that peripheral blood progenitor cells at diagnosis could efficiently be used to reconstitute hematopoiesis after similar conditioning. The results of ASCT for CML in transformation have been extensively reviewed and can be summarized as follows. First, hematopoietic recovery is faster after peripheral blood than bone marrow stem cell transplantation. Second, following ASCT, some patients exhibit a cytogenetic conversion due to the re-emergence of Ph-negative cells and they seem to have prolonged survival. Third, unsurprisingly, the survival of patients transplanted in accelerated phase is longer than that of those transplanted in blast crisis. Fourth, patients treated with interferon (IFN) after transplant survive longer than others. Finally, a second chronic phase is obtained in most cases but its duration is usually short, as most patients develop a recurrent blast crisis within 6-9 months due to the clone implicated in the first transformation.

Thus, in most patients with advanced disease restoring a prolonged second chronic phase has not proven possible, and so ASCT has progressive-ly been abandoned for patients with CML in transformation.

Autografting in chronic phase: rationale

Autografting in chronic phase (CP) is now becoming increasingly used as some preliminary results suggest that ASCT could increase the proportion of patients with a cytogenetic response, and thus prolong survival. Since it is well known that the reinfused material contributes to the reappearance of the disease, the rationale for autografting in chronic phase resides in the reduction of the tumor burden and the number of leukemic cells at risk of developing a second genetic event responsible for the blastic transformation. This, in turn, would delay the emergence of a blastic phase and prolong survival. A second possibility is a setting back the clock effect by which the cells that have already mutated are eradicated and new, fresh, non-transformed cells replace them after the transplant. Thirdly, there is the possibility of reverting IFN resistance so that IFN can achieve a cytogenetic response when used after autografting in patients previously resistant to IFN. More recently, the group in Genoa has shown the feasibility of collecting Ph-negative stem cells after in vivo purging with chemotherapy (mini-ICE). These normal Ph-negative cells can be used in an autografting procedure and most patients recover with Ph-negative hematopoiesis.

Choice of progenitor cells

Although in the early years most stem cell transplants (SCT) were performed with bone marrow material, the vast majority of transplants today are done with peripheral blood stem cells (PBSC). The advantages of PBSC include more feasibility and easier collection, increased numbers of stem cells collected, the possibility of multiple collections and the option of collecting stem cells after different therapies. Several attempts have been made to collect stem cells following treatment with IFN in patients with some degree of cytogenetic response and then use them unmanipulated for autografting.

In this number of Haematologica, Hernandez-Boluda et al. describe their experience with the use of IFN as an in vivo purging agent. They demonstrate that a successful stem cell harvest is feasible in the majority of patients. These cells were successfully used in autografting 4 patients. Granulocyte colony-stimulating factor (G-CSF) was well tolerated and produced no effect on the Ph-positive clone since in all patients the same level of cytogenetic response persisted after the procedure.
Autografting in chronic phase: the EBMT survey

Many single center and multicenter studies have now been published.\textsuperscript{7,12-16} Not surprisingly, results of the retrospective analysis of multicenter studies correspond to those of single center studies. In a recent survey of the EBMT database, 581 patients with CML in chronic phase had been reported to have undergone an autologous SCT for the first time.\textsuperscript{17} The median follow-up at the time of analysis was 18 months. The median age at SCT was 44 years. The interval between diagnosis and SCT was 20 months. Most patients were transplanted after more than 12 months in chronic phase and the majority had been treated with IFN before SCT. Sixty-seven per cent of IFN-treated patients were refractory at the chromosomal level and one third were classified as having high-risk disease. The transplant procedure was performed using peripheral blood cells alone in more than 70% of cases. Most centers used busulfan alone or in combination with cyclophosphamide or melphalan in the preparative conditioning although 60 patients received total body irradiation. There has been an increase in the numbers of autografts performed with mobilized stem cells in recent years with nearly 100 cases reported in this survey between 1994-1998. The overall transplant mortality was low (4.6%) and seemed to be greater in transplants done with bone marrow stem cells and/or TBI. It was less than 1% for patients transplanted soon after diagnosis. The overall survival was 65% at 5 years from transplant with more than 50% of all patients remaining in chronic phase at 5 years. The use of IFN post-autograft was beneficial with more than 80% of patients treated with IFN after SCT surviving at 3 years compared with 55% if they were not given IFN post-SCT. Patients transplanted within 6 months from diagnosis and treated with IFN after hematologic recovery had an extremely good prognosis with more than 85% being alive 5 years after their transplant.

Toxicity and post-SCT therapy

ASCT performed during CP has a low toxicity (as the transplant-related mortality does not exceed 5% in most series). The mortality seems higher in patients transplanted with bone marrow cells and receiving TBI. Most centers now use chemotherapy only (such as busulfan-cyclophosphamide or busulfan-melphalan or even busulfan alone) with similar results and a reduced toxicity. Hematopoietic reconstitution using peripheral blood stem cells is usually rapid (less than 15 days), and the five-year survival from transplantation varies between 50-70%. These results compare favorably with results after allogeneic SCT. However, unlike after the latter, almost all patients have persistent disease after ASCT.

Thus, ASCT is not a curative treatment for CML but could restore IFN sensitivity and prolong survival.\textsuperscript{18} In the EBMT retrospective analysis, there is a suggestion that patients previously resistant or refractory to IFN could obtain a cytogenetic remission after autografting and more importantly, maintain the cytogenetic response when IFN is used after SCT. Fifteen per cent of IFN refractory patients could expect to achieve a complete cytogenetic remission and 20% a major response. Furthermore, survival seems to be prolonged in those patients maintaining a cytogenetic response to IFN post-SCT for at least 12 months.

While ASCT might be able to prolong survival, it is important to know which category of patients with CML in chronic phase could benefit from ASCT. For patients responding to IFN, and especially those who achieve a major or complete cytogenetic response (≥65% Ph-negative cells), the probability of surviving for five years is 90%.\textsuperscript{14,19-21} For these patients, it would be very difficult to demonstrate a survival advantage for ASCT. As most of these IFN-responding patients do not have a high Sokal index, it could be that ASCT is indicated only for patients with high-risk CML. In France ASCT was performed in 20 CML patients with a Sokal index > 1.2. These patients were given busulfan and melphalan and were then reinfused with blood stem cells. Sixteen of them received IFN after ASCT and three achieved a major cytogenetic response.\textsuperscript{4,18} The results have been recently updated: 8 of the 20 patients are still alive 56 to 166 months after transplantation. In the EBMT survey, 52 patients (high-risk disease) were autografted early after diagnosis (27 patients) or in late chronic phase (25 patients) with a trend to a better survival for patients autografted early (72% versus 39% survival at 5 years).\textsuperscript{17}

Final considerations

In summary, retrospective and single center trials have shown that autologous SCT in CML could prolong survival if performed in chronic phase. Unfortunately, no randomized trial has been conducted to compare outcome after autografting with IFN-based therapy. Results from the French and Italian groups showed that similar results can be obtained with a combination of IFN and Ara-C. It is, therefore, important that such a comparison
is made. Several national groups (SGFM, GETH, German CML III study group, MRC, ECOG) have initiated randomized trials comparing different forms of autografting with IFN. More recently the EBMT has launched a multicenter, multinational study comparing autografting with IFN. This trial is going to include the French, Spanish and British initiatives and will be analyzed together with the second randomization of the German CML III-A trial in a meta-analysis.

IFN can result in some degree of cytogenetic response in more than 40% of patients and, according to the study by Hernandez-Boluda et al. and other observations, it is possible to collect Ph-negative stem cells in the majority of these patients. Imatinib mesylate (STI571), a tyrosine kinase inhibitor, preferentially inhibits proliferation of Ph-negative cells. It is capable of inducing major cytogenetic responses in more than 50% of patients refractory to IFN. Results in newly diagnosed patients are expected to be even better. Collection of Ph-negative cells from patients treated with STI571 is feasible although complicated. Today, it seems that a substantial number of patients with CML could be autografted with Ph-negative material.

The development of new tyrosine kinase inhibitors has changed our understanding of the pathophysiology of CML. It is possible that, with the advent of STI-571 and other tyrosine kinase inhibitors, the role of autografting in the management of CML will have to be re-defined. It is also possible that the combination of all three therapeutic strategies (protein inhibition with STI-571, immunomodulation with IFN and chemoreduction with SCT) either concomitantly or sequentially will lead to a higher proportion of patients surviving long-term.

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References

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Efficacy and safety of aspirin in the long-term management of atherothrombosis

The role of aspirin and other platelet-active drugs in the treatment and prevention of atherothrombosis has been reviewed by the Sixth ACCP Consensus Conference on Antithrombotic Therapy. Moreover, additional information on the efficacy and safety of antiplatelet therapy is provided by the recent collaborative meta-analysis of 266 secondary prevention trials, prepared by the Anti-thrombotic Trialists’ (ATT) Collaboration. What follows is a brief update of these important documents.

Balance of benefits and risks

The absolute benefits of aspirin therapy substantially outweigh the absolute risks of major bleeding (particularly, gastrointestinal) complications in a variety of clinical settings characterized by moderate to high risk of occlusive vascular events (Table 1). However, in low-risk individuals the benefit/risk profile of such a preventive strategy is uncertain. Thus, a very small absolute benefit may be offset by exposure of very large numbers of healthy subjects to undue bleeding complications. The risk of upper gastrointestinal bleeding (UGIB) associated with medium-to-high doses of aspirin can be reduced to a relative risk of 2.0 vs non-users by using the lowest effective dose of the drug (ie 75 to 160 mg daily). However, this risk can not be further reduced by other strategies since it is most likely related to the antiplatelet effect of aspirin, which is largely dose-independent for daily doses in excess of 30 mg. Thus, recent studies have attempted to determine which groups of patients may derive particular benefit or experience harm from the use of low-dose aspirin for the primary prevention of ischemic heart disease. Subgroup analysis of the Thrombosis Prevention Trial suggests that the benefit of low-dose aspirin may occur mainly in those with lower systolic blood pressures, although it is not clear even in these men that the benefit outweighs the potential hazards. A recently discontinued trial of low-dose aspirin in general practice failed to demonstrate a clearly favorable benefit/risk profile in men and women aged 50 years or older with one or more major cardiovascular risk factors.

A meta-analysis of four primary prevention trials suggests that aspirin treatment is safe and worthwhile at coronary event risk equal to or greater than 1.5% per year. The ATT Collaboration is currently conducting an overview of all randomised trials of aspirin vs placebo in low-risk subjects, based on individual patient data.

Aspirin resistance

The issue of aspirin resistance continues to be debated. This term has been used to describe a number of different phenomena, including the inability of aspirin to do the following: 1) to protect individuals from thrombotic complications; 2) to cause a prolongation of the bleeding time; or, 3) to produce an anticipated effect on one or more in vitro tests of platelet function. Based on measurements of optical platelet aggregation in response to archidonic acid and ADP, 5% and 24% of patients with stable cardiovascular disease who were receiving aspirin (325 mg/day for ≥ 7 days) were defined as resistant and semi-responders, respectively. However, the lack of appropriate controls in this study (e.g., patients treated with anoth-
er antiplatelet agent) precludes unequivocal interpretation of these findings. A recent report suggests that cyclo-oxygenase (COX)-2 expression in circulating platelets may contribute to this phenomenon. Kawasaki et al. have recently reported that prior administration of non-aspirin NSAIDs may actually underestimate the absolute risk in an elderly population exposed to “primary” prevention. The absolute excess of major bleeding complications in the “primary” prevention trials reviewed in ref. #1 ranged between 0.3 and 1.7 per 1,000 patient-years. Reproduced from Patrono et al., Chest 2001 (ref. #1).

### Table 1. Benefit/risk ratio of antiplatelet prophylaxis with aspirin in different settings.

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Benefit* Number of patients in whom a major vascular event is avoided per 1,000/year</th>
<th>Risk* Number of patients in whom a major GI bleeding event is caused per 1,000/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men at Low to High Cardiovascular Risk</td>
<td>1-2</td>
<td>1-2</td>
</tr>
<tr>
<td>Essential Hypertension</td>
<td>1-2</td>
<td>1-2</td>
</tr>
<tr>
<td>Chronic Stable Angina</td>
<td>10</td>
<td>1-2</td>
</tr>
<tr>
<td>Prior Myocardial Infarction</td>
<td>20</td>
<td>1-2</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>50</td>
<td>1-2</td>
</tr>
</tbody>
</table>

*Benefits are calculated from randomized trial data reviewed in reference 1; *risks of upper GI bleeding are estimated from a background rate of 1 event per 1,000 per year in the general population of non-users and a relative risk of 2.0 to 3.0 associated with aspirin prophylaxis. Such an estimate assumes comparability of other risk factors for upper GI bleeding, such as age and concomitant use of NSAIDs, and may actually underestimate the absolute risk in an elderly population exposed to “primary” prevention. The absolute excess of major bleeding complications in the “primary” prevention trials reviewed in ref. #1 ranged between 0.3 and 1.7 per 1,000 patient-years. Reproduced from Patrono et al., Chest 2001 (ref. #1).

In conclusion, patients at moderate to high cardiovascular risk (e.g., those with chronic stable

be insufficient to block platelet aggregation adequately in vivo, because of the very substantial biosynthetic capacity of human platelets to produce TXA2. In fact, in a prospective population-based observational study of approximately 165,000 post-menopausal women, chronic use of non-aspirin NSAIDs was not associated with a protective effect against the risk of a first myocardial infarction (MI) (RR=1.32; 95% CI, 0.97-1.81). Because non-aspirin NSAIDs have been inadequately investigated in terms of their potential cardiovascular effects, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue low-dose aspirin, even though concomitant administration of the two may amplify the risk of upper GI bleeding.

The cardiovascular safety of selective COX-2 inhibitors (coxibs) in arthritic patients at low cardiovascular risk is currently being debated, based on the recently reported results of two relatively large GI safety studies, VIGOR and CLASS, with short follow-up and inadequate statistical power to detect a realistic difference – one way or the other – in vascular end-points between coxibs and conventional NSAIDs. At least three possible explanations can be entertained in accounting for the statistically significant difference in MI between rofecoxib and naproxen (0.4% vs 0.1%), as reported by the VIGOR trial: 1) a cardioprotective effect of naproxen; but, there is no convincing evidence that conventional NSAIDs reduce the risk of MI at prescribed doses; moreover, it is unlikely that they inhibit platelet COX-1 by greater than 95% throughout the dosing interval; 2) a thrombogenic effect of coxibs; but, the size of the effect is not biologically plausible if due to incomplete inhibition of a single mediator of thromboresistance, i.e. prostacyclin (PGI2); moreover, such an explanation is not substantiated by the CLASS results, though a smaller coxib effect cannot be excluded; 3) the play of chance; the apparent difference in VIGOR might represent an uneven distribution of a small number of events occurring over a short time frame in a low-risk population, as suggested by a recent meta-analysis of all rofecoxib trials. An independent overview of all randomized comparisons between any coxib (celecoxib, rofecoxib, etoricoxib, valdecoxib and COX-189) and any non-selective NSAID appears to offer a feasible strategy to answer this question, and one that would not require a very large head-to-head randomized trial with vascular end-points.

In conclusion, patients at moderate to high cardiovascular risk (e.g., those with chronic stable

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angina, prior MI or stroke/transient ischemic attacks) should be prescribed low-dose aspirin (75-100 mg daily) because its potential benefit clearly outweighs the risk of serious bleeding complications.\textsuperscript{1,2} Should these patients require NSAID therapy, safety considerations as well as the lack of pharmacodynamic interactions with low-dose aspirin\textsuperscript{10} would favor a specific COX-2 inhibitor over conventional NSAIDs. Patients at low cardiovascular risk (ie those without a prior vascular event) are not likely to be prescribed low-dose aspirin because of the uncertain benefit/risk profile of such a strategy in this setting. In these patients, the absolute benefit to be derived from inhibition of COX-2-dependent PG\textsubscript{I}2 biosynthesis\textsuperscript{12} is likely to outweigh any potential harm to be derived from inhibition of COX-2-dependent PG\textsubscript{I}2 biosynthesis.\textsuperscript{12}

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References
Background and Objectives. Myelodysplastic syndromes (MDS) comprise a group of heterogeneous hematologic disorders with risk of leukemic evolution (LE). The French-American-British (FAB) cooperative group classifies them into five morphologic entities and the International Prognostic Scoring System (IPSS) proposes four groups of risk on the basis of clinical and cytogenetic variables. The aim of this study was to evaluate the application of the IPSS in our Argentine population, to test the prognostic value of its variables and to determine whether this score helps to associate prognostic subgroups of risk into FAB subtypes.

Design and Methods. Two hundred and thirty-four patients with primary MDS and a median follow-up of 28 months were evaluated using univariate analyses to determine median survival (SV) and the time to LE. The variables analyzed were FAB classification, IPSS, percentage of myeloblasts, cytogenetic groups of risk and number of cytopenias.

Results. Univariate analyses showed that all variables analyzed were predictive for SV and for LE in our MDS population. Application of the IPSS allowed discrimination into the 4 groups of risk and helped to identify prognostic subclasses among the FAB classification, associating 5%, 15% and 19% of cases with worse prognosis within the FAB classification of refractory anemia (RA), RA with ringed sideroblasts and RA with excess of blasts (RAEB), respectively. The IPSS was not informative for RAEB in transformation cases and would not be applied to patients with chronic myelomonocytic leukemia.

Interpretation and Conclusions. This score could be applied to our MDS population, showing no geographic differences. Stratification of FAB patients according to IPSS would be helpful to develop risk-adapted therapeutic strategies. © 2002, Ferrata Storti Foundation

Key words: myelodysplastic syndromes, IPSS, prognostic variables, leukemic evolution.