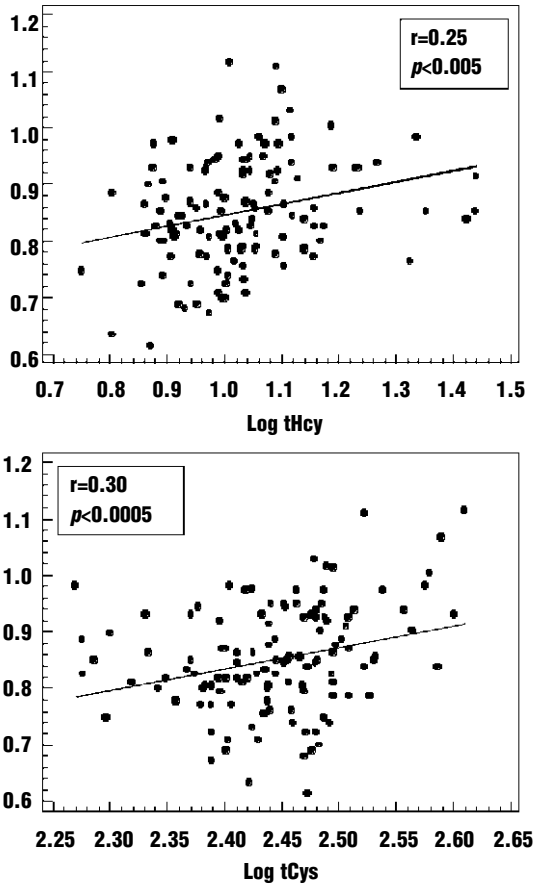

Figure 1. Univariate Pearson's correlation between WBC count and cysteine and homocysteine levels after the log transformation of all data (n=124).

by thiol (-SH) auto-oxidation. Although less reactive than homocysteine, cysteine shares some of the chemical properties derived from the presence of the sulfhydryl group. Cysteine has a general cytotoxicity *in vitro* and promotes the detachment of human arterial endothelial cells in culture. It also exhibits auto-oxidation properties in the presence of metal ions, resulting in the generation of free radicals and hydrogen peroxide that promote the activation of the cellular immune system by enhanced induction of NF-κB and MCP-1. Finally cysteine can support superoxide-mediated modification of low density lipoproteins (LDL), thus facilitating the formation of foam cells. In conclusion this study provides additional experimental evidence suggesting a strong association between serum levels of cysteine and homocysteine and blood cells *in vivo*. However further studies are required to understand whether rising serum thiols levels are the trigger for the WBC increment, thus promoting or contributing to the pro-inflammatory and pro-atherosclerotic responses.

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Thrombosis

Oral vitamin K produces a normal INR within 24 hours of its administration in most patients discontinuing warfarin

A randomized, blinded study in 30 patients was undertaken. This study found that low dose oral vitamin K was more effective than placebo when used to correct the INR in patients who are discontinuing warfarin. Larger studies will be required to determine if the use of oral vitamin K, for example in patients who are temporarily discontinuing warfarin to undergo interventional procedures, is safe and effective.

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Warfarin is the only long-term oral anticoagulant available but must be stopped in the peri-operative period. To minimize the risk of thromboembolism during this period, patients who require interruption of their warfarin therapy often receive *bridging a*nticoagulant therapy with a low molecular weight heparin.[1] The ability of oral vitamin K return the INR to the target range in over-anticoagulated patients suggests that it might be useful to normalize the INR in the peri-operative setting. Administering a small dose of oral vitamin K 24 to 48 hours prior to the procedure may shorten the time period during which patients are not receiving warfarin thus obviating the need for bridging therapy. Before such a treatment strategy is widely adopted there must be evidence that oral vitamin K therapy satisfies the following criteria: (A) the INR falls reliably into a range that is considered safe for surgery in a high proportion of patients, (B) the levels of the vitamin K-dependent coagulation factors increase in response to vitamin K in a manner which suggests that

Table 1. Patients' characteristics.

	Vitamin K N=15	*Placebo N=15*
Age (yrs)	69	67
Gender (No. female)	9	9
Weight (kg)	78	84
Clinical Centre (No. in Hamilton)	10	10
Mean (range) Day 0 INR	2.6 (0.9 to 6.2)	1.9 (1.0 to 2.9)
Change in INR (Day 0 to day 1)	1.3 INR units	0.2 INR units
Mean INR on study day 1 (range)	1.3 (0.8 to 1.8)*	1.7 (0.9 to 2.5)*
Mean INR on study day 2 (range)	1.1 (0.9 to 1.7)°	1.4 (1.0 to 1.8)°
Number of patients with INR less than 1.4 on day following vitamin K	10	6

**p value of comparison of day 1 INR between groups p = 0.02; °p value of comparison of day 2 INR between groups p = 0.003.*

the integrity of the coagulation cascade has been restored, and (C) vitamin K does not cause warfarin resistance. To address the first two of these criteria we performed a randomized trial.

Eligible patients had received warfarin for more than 30 days with a target INR between 2.0 and 3.0, and were stopping warfarin. Patients were excluded if urgent INR correction was required, if they were allergic to vitamin K, if they could not provide serial blood samples for analysis, or if they failed to provide written informed consent. Ethics Board approval for the protocol was obtained. Eligible, consenting patients were given either 2.5 mg of oral vitamin K or a matching placebo. Randomization was stratified by centre. Participating investigators, laboratory personnel and patients remained masked to treatment allocation throughout the study. Plasma samples were analyzed for: (1) PT/INR, using Innovin (Dade Behring, Mississauga ON, USA); (2) functional levels of factors II, VII and V, using commercial deficient plasma from BioMeriuex (Durham, NC, USA) and Innovin. Results were reported in units/mL. Between May 2002 and May 2003, 30 patients were enrolled from the Department of Medicine at St. Joseph's Hospital, Hamilton, Ontario, Canada, and the Department of Medicine at the Ospedale di Circolo, Varese, Italy (Table 1).

The INR in the placebo group declined by 0.26 INR units (from 1.94 to 1.68), compared with 1.31 INR units in the vitamin K group (from 2.58 to 1.27, p=0.007) (Table 1). The INR values were significantly lower in the vitamin K group on each of the 5 days of the study. On the day after study drug 6 of 15 patients allocated to placebo, compared with 10 of 15 allocated to vitamin K, had an INR less than 1.4. Coagulation factor levels are presented in Figure 1a-c.

One patient who received vitamin K had recurrent, objectively confirmed deep vein thrombosis on day 12 while one patient who received placebo had recurrent superficial venous thrombosis on day 20.

We found that patients who received oral vitamin K had a significant reduction in their INR values between the day of study drug administration and the day following. Our observation that the INR is reduced to the normal range in a high proportion of patients within 24 to 48 hours of the administration of low-dose oral vitamin K provides preliminary evidence to support its further evaluation in a

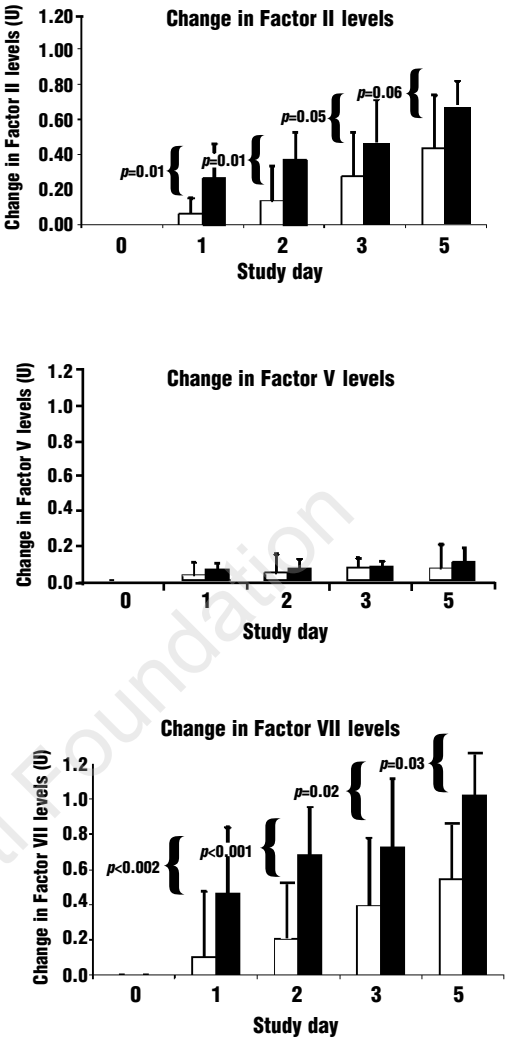

Figure 1. Changes in coagulation factor levels in patients allocated to vitamin K (solid bars) and placebo (open bars) are presented for each day of the study.

large clinical trial. Use of oral vitamin K as an agent to normalize the INR is further supported by a recent randomized trial[2] which found that oral and intravenous vitamin K are similarly effective at reducing the INR, if changes in the INR at 24 hours after administration is the endpoint of interest. Low doses of oral vitamin K may prove appropriate for patients who require correction of their INR during the 24 to 48 hours prior to surgery or other interventions. However, before strategies which substitute vitamin K administration for early discontinuation of warfarin with low molecular weight heparin *bridging* are adopted, the safety and efficacy of such strategies will need to be tested in well-designed studies.

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Stem Cell Transplantation

Autologous stem cell transplantation for acute myeloid leukemia patients in first complete remission: a 10-year follow-up study of 118 patients

We assessed the impact of unpurged autologous stem cell transplantation (ASCT) on long-term outcome of 118 patients with acute myeloid leukemia (AML) in first complete remission (CR1). With a median follow-up of 95 months, the 10-year overall survival, disease-free survival and relapse risk are, respectively, 54%, 50% and 46%. *De novo* AML, the presence of a favorable karyotype and intensification of treatment prior to ASCT are independently associated with clinical outcome by multivariate analysis. Thus, a remarkable proportion of AML patients in CR1 can be cured with high-dose therapy and ASCT.

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The role of autologous stem cell transplantation (ASCT) in the treatment of patients with acute myeloblastic leukemia (AML) in first complete remission (CR1) remains unsettled. Phase II and III trials showed that ASCT provides lower relapse rates than conventional chemotherapy and improves disease-free survival (DFS) in some but not in all studies.[1-3] We studied the long-term outcome of 118 AML patients in CR1 treated in a single institution between January 1990 and December 2001 (Table 1). Karyotype was considered as: (i) favorable [t (8;21) or inv(16)]; (ii) intermediate (diploid, insufficient metaphases, or a single numerical abnormality other than that defined as unfavorable); (iii) unfavorable (ie trisomy 8, abnormalities of chromosome 5 and/or 7, abnormality of chromosome 11, multiple or complex translocation).[4] Induction chemotherapy consisted of the standard 3/7 daunorubicin/cytosine arabinoside regimen from January 1990 to December 1992[5] and idarubicin/cytosine arabinoside/etoposide from January 1993 until the end of the study.[6,7] All patients, independently from disease status after induction, received one or two courses of consolidation chemotherapy. Overall, 70 patients (66%) received 2 cycles of treatment whereas 48 patients (34%) received 3 cycles before ASCT.

The median time from CR1 to stem cell collection was 3 months (range: 2-16). The source of stem cells was the bone marrow (BM) for the patients treated before 1993 and for those who did not mobilize peripheral blood stem cells (PBSC) after fludarabine-containing consolidation regimens (N=80) and mobilized PBSC for the remaining 38 patients. A minimum number of 1×10^8 nucleated cells/kg or 1×10^6 $CD34^+$ cells/kg was required to proceed to BM or PBSC transplantation, respectively. ASCT was performed at a median of 7 months after diagnosis (4-19) and 6 months (3-16) after CR1. The conditioning regimen before ASCT always included oral busulfan (16 mg/kg). A median number of total nucleated cells of 2.3×10^8/kg were reinfused. A proportional hazards regression model was used to investigate overall survival (OS), DFS and time to relapse (TTR). Variables showing a *p*-value d 0.05 in univariate analysis were included in the final model for the multivariate analysis.

The feasibility of ASCT for AML patients in CR1, the hematologic recovery and early outcome have been previously reported.[5-8] The incidence of transplant-related mortality (TRM) was 1.7% whereas the overall nonrelapse mortality was 4.2%. The median follow-up for surviving patients is 95 months (range: 24-162). Sixty-five patients are alive including 61 patients in continuous CR1. The 10-year OS is 54.6% (95% confidence interval: 45.3-63.9). The 10-year DFS is 50.7% (95% confidence interval: 41.4-59.9). A total of 51 patients relapsed at a median of 7 months after ASCT (range: 2-76). The 10-year cumulative incidence of relapse is 46.2% (95% con-

Table 1 Patients' characteristics.

Number of patients	118
Median age (range)	49 (16-66)
Gender (M/F)	58/60
Secondary leukemia (%)	20 (17%)
FAB classification	
M0/M1	38 (32%)
M2	29 (25%)
M4	34 (30%)
M5	15 (12%)
M6/M7	2 (1%)
WBC at diagnosis:	
Median $x10^9$/L (range)	11.3 (0.74 - 329)
Patients with WBC $\geq30x10^9$/L	35 (30%)
Karyotype	
Favorable	20 (17%)
Intermediate	63 (55%)
Unfavorable	30 (25%)
Unknown	5 (4%)
Number of cycles prior to ASCT*	
2	70 (60%)
3	48 (40%)

Induction chemotherapy was: 1) standard 3/7 daunorubicine/citosine arabinoside regimen (Dauno/ARA-C) [Dauno 45-60 mg/m²/day (days 1-3) and Ara-C 100 mg/m²/day by continuous iv infusion (days 1-7)] from January 1990 to December 1992 (N=42); 2) ICE regimen [idarubicin 10 mg/m²/day (days 1,3,5), Ara-C 100 mg/m²/day by continuos iv infusion (days 1-10) and etoposide 100 mg/m²/day (days 1-5)] from January 1993 until the end of the study (N=76). Three different consolidation regimens were adopted, depending on the study period: 1) two courses of standard 3/7 Dauno/Ara-C from January 1990 to December 1992 (N=42); 2) a single NOVIA consolidation cycle [Ara-C 500 mg/m²/twice a day (days 1-6) and mitoxantrone 12 mg/m2/day (days 4-6) from January 1993 to June 1996 (N.=32); 3) double FLAN consolidation therapy [fludarabine 30 mg/m²/day iv (days 1-5), Ara-C 2 g/m²/day (days 1-5) and mitoxantrone 6 mg/m²/day (days 1-3) from July 1996 to December 2001 (N=44).