An excess of AML FAB M7 is well documented in DS: it is a unique disease associated with a pathognomonic mutation of GATA1.[9] This report supports the separate pediatric WHO classification of myeloid leukemia of DS (ML-DS).[10] It is notable that subtypes were reclassified in 6/14(43%) cases of DS-AML. Unfortunately, this does not appear to be reflected in an earlier report of DS cases in the MRC AML 10 and 12 trials,[11] which appears to rely on the initial classifications, highlighting the importance of ensuring data is as comprehensive and up to date as possible. Here, the final AML subtypes were exclusively FAB M6 and M7. Although an apparent excess of AML M6 has also been reported, the association is not so clearly described.

A report considering trial cases alone for this period would have missed a third of all cases of acute leukemia in DS, and almost half of all cases of AML in DS. The relatively low entry of children with DS into trials limits the utility of reports solely derived from trials, emphasizing the need for a population based approach until trial entry rates have improved. Reports suggest that these are increasing, reflecting a growing recognition that children with DS may be successfully treated with intensive chemotherapy and in the context of a trial. There is a pressing need for a collaborative effort to gather data prospectively on all children with DS. The Children with Down's Syndrome Study (*www.cdss.org.uk*) is an observational cohort study set up specifically to address this need and will enable determination of the baseline characteristics of all children with DS. Furthermore, until trial entry improves, a population based approach is also imperative for the study of children with both DS and leukemia.

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Key words: acute leukemia, acute myeloid leukemia, myelodysplasia, myeloproliferative disorders, Down's syndrome.

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Kinetics of bone marrow blasts during induction and achievement of complete remission in acute myeloid leukemia

In acute myeloid leukemia (AML), bone marrow is typically examined 14 days after beginning initial induction therapy. If significant residual blasts remain, the National Comprehensive Cancer Network (NCCN) Guidelines for AML recommend re-treatment.[1] Here we examine whether bone marrow findings on day 21 might modulate the day 14 findings and thus influence the decision to begin a second course.

Our database comprised those 586 adults who had both day 14 and day 21 bone marrows (±2 days) after receiving, from 1995 to 2004, cytarabine (≥1g/m^2 per day) -con-

taining therapy for newly diagnosed AML. Their median age was 60 years. Six percent had inv(16)/t(16;16) or t(8;21), 33% had abnormalities of chromosomes 5 and/or 7 or complex karyotype, and 61% had other findings. In addition to high-dose cytarabine, induction therapy contained idarubicin without fludarabine or topotecan in 18%, fludarabine with or without idarubicin in 35%, and topotecan without idarubicin in 32%, and other therapies in 15%.[2] This study was approved by the M.D Anderson Institutional Review Board, and patients were treated in accordance with the Declaration of Helsinki.

Bone marrow status was defined as "too few cells to count (TFTC)" if the total cell count was less than 100 after reviewing 4 slides. Complete remission (CR) was defined by a bone marrow with <5% blasts, a neutrophil count ≥1×10^9/L and a platelet count ≥100×10^9/L. Groups were compared using Fisher's exact test for categorical variables, and the Wilcoxon rank-sum test for numerical variables.

Three-hundred and seventy-five patients (64%) achieved CR on course 1. A second course with a similar regimen was given to 64 patients, and resulted in CR in an additional 19 patients. As expected, the probability of CR on course 1 decreased as the percentage of blasts in either the day 14 or the day 21 marrow increased, such that only a minority of patients who had ≥20% blasts on either date entered CR on this course (Table 1). Of most interest are the probabilities of course 1 CR according to the combination of the day 14 marrow with the day 21 marrow (Table 2). In particular, 37 of the 72 patients (51%) with 20-59% blasts on day 14 had <20% blasts on day 21, and 23 of the 37 (62%) entered CR on course 1 without further therapy. In contrast, patients with 20-59% blasts on day 14 whose day 21 marrow did not improve had a course 1 CR rate of only 8/26 (31%); TFTC on day 21 after 20-59% blasts on day 14 was not advantageous (CR rate 2/7). Thirty out of 37 (81%) patients with ≥60% blasts on day 14 continued to have ≥20% blasts on day 21 and the course 1 CR rate in these patients was only 7%, and was only 16% for all patients with ≥60% blasts on day 14 regardless of the day 21 findings. Patients with TFTC or <20% blasts in the day 14 marrow but whose day 21 marrows had ≥20% blasts seemed less likely to achieve CR, but such cases accounted for only 12% and 11% of each group. In all groups described above, failure to enter CR typically reflected resistance to therapy rather than death before response could be evaluated (eg. before day 35).

Previous studies have shown a significant correlation between the percentage of blasts in early bone marrow and the subsequent probability of CR.[3-6] However, most such reports analyzed patients who received double induction (DI) therapy[3,5,6] in which a second course was given regardless of the percentage of bone marrow blasts, so that CR was evaluated after the second course. In patients not given DI, however, a decision must be made whether to start a second course or to wait for recovery; hence evaluation of early bone marrow is more important. The NCCN guidelines recommend that the decision be guided by bone marrow 7-10 days after completion of induction therapy.[1] However, clinical experience suggests that patients with a high blast percentage in early bone marrow can enter CR without further therapy, prompting us to investigate whether the day 21 marrow adds useful information to the day 14 marrow. Our results show that the day 21 marrow does not materially alter the decision to begin course 2 as based on the day 14 marrow in patients with TFTC, <20% blasts, or ≥60% blasts in the day 14 marrow. However, approximately half of patients with 20-59% blasts in the day 14 marrow will have <20% blasts on day 21 and in these patients the probability of CR without administering a second course seems sufficiently high (62%) to warrant, in at least some patients, delaying a second course until the day 21 marrow can be examined.

This conclusion is subject to several criticisms. First, our patients uniformly received cytarabine at doses considerably above those used in 3+7. Accordingly, the proportion of patients given 3+7 who have 20-59% blasts on day 14 but who have <20% blasts on day 21 might be less than the 51% noted here. Second, not all our patients who

Table 1. Probability of complete remission according to bone marrow findings on days 14 and 21.

Blasts (%)	*Day 14 marrow*		*Day 21 marrow*	
	N. of CR/non-CR	*% CR*	*N. of CR/non-CR*	*% CR*
TFTC	254/105	71%	71/54	57%
0-4	47/15	76%	175/39	82%
5-9	13/7	65%	49/14	78%
10-19	22/14	61%	50/22	69%
20-29	12/13	48%	16/20	44%
30-39	9/11	45%	9/16	36%
40-49	6/9	40%	2/11	15%
50-59	6/6	50%	3/8	27%
60-69	2/12	14%	0/11	0%
70-79	2/8	20%	0/5	0%
80-89	0/8	0%	0/6	0%
90-100	2/3	40%	0/5	0%
Total	375/211	64%	375/211	64%

CR: complete remission; TFTC: too few cells to count (<100 cells counted after reviewing 4 smears).

Table 2. Probability of complete remission according to combination of bone marrow findings on days 14 and 21.

Day 14 bone marrow	*Day 21 bone marrow*	*N. of CR/non-CR*	*% CR*
TFTC	TFTC	65/45	59%
	<20% blasts	172/35	83%
	20-59% blasts	17/17	50%
	≥60% blasts	0/8	0%
	Total	254/105	71%
<20% blasts	TFTC	3/4	43%
	<20% blasts	76/23	77%
	20-59% blasts	3/8	27%
	≥60% blasts	0/1	0%
	Total	82/36	69%
20-59% blasts	TFTC	2/5	29%
	<20% blasts	23/14	62%
	20-59% blasts	8/18	31%
	≥60% blasts	0/2	0%
	Total	33/39	46%
≥60% blasts	TFTC	1/0	100%
	<20% blasts	3/3	50%
	20-59% blasts	2/12	14%
	≥60% blasts	0/16	0%
	Total	6/31	16%

CR: complete remission; TFTC: too few cells to count (<100 cells counted after reviewing 4 smears).

were alive on day 14 or day 21 had a marrow examined then. Third, we did not examine marrow cellularity, feeling that this might be particularly susceptible to inter-observer variability. Finally, delaying until day 21 in patients with 20-59% blasts on day 14 might not affect CR rate, but might shorten CR duration. However, this risk has to be weighed against the competing risk of giving a second induction course, particularly to older patients. Specifically, while there will be myelosuppression on either a second induction course or a first post-remission course, the risk of infection at any given neutrophil count is less when a patient is in CR than when not, and duration of neutropenia is often less in patients in CR. Hence in older patients physicians might prefer to wait until CR to re-treat. Our data make the option of delay more plausible and suggest the need to revisit the NCCN recommendations in patients given 3+7.

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Key words: acute myeloid leukemia, bone marrow blasts, complete remission.

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Lack of prognostic value of *FCGR3A*-V158F polymorphism in non-Hodgkin's lymphoma

Recently it was shown that the therapeutic efficacy of the anti-CD20 monoclonal antibody rituximab might be influenced by single nucleotide polymorphisms in the Fcγ receptor IIIa gene (*FCGR3A*).[1-3] Binding of the Fc (constant) region of immunoglobulin G1 (IgG1) to the FcGRIIIa on the surface of natural killer (NK) cells or macrophages triggers antibody-dependent cellular cytotoxicity (ADCC), inducing B-cell elimination. The *FCGR3A*-158 valine (V) allele has a higher affinity for IgG1 than the phenylalanine allele (F) and mediates ADCC more effectively.[4] Homozygous 158V follicular lymphoma patients were found to have better responses to single agent rituximab[1,3] and longer progression free survival.[2,3]

Fcγ receptor polymorphisms can also influence the immune response to auto-antibodies and have been shown to be risk factors in autoimmune disease.[5] In lymphoma patients, auto-antibodies to antigens expressed on lymphoma cells have been identified[6] and effector cells that express polymorphic *FCGR3A*-158, may also have altered binding to these antibodies that could influence host response and disease progression independent of rituximab therapy. In addition, a recent investigation has demonstrated that individuals expressing *FCGR3A*-158VV and VF show greater NK cell surface expression of *FcGRIIIa* receptors than the FF types.[7]

Few studies have examined a statistically large enough group of non-Hodgkin's lymphoma (NHL) patients to determine if VV patients have a biologically different disease or survival advantage when treated only with chemotherapy or radiation. We selected patients from 291 newly diagnosed NHL patients who were entered into our prospective biological prognostic factor study between 1990-1995. The Human Subjects Review Committee at the University of Toronto and the appropriate committees at Sunnybrook Health Science Centre approved the study. All patients provided informed consent. We studied the 194 patients who had sufficient information for a detailed multivariate analysis with five factors including grade, tumor bulk, International Progostic Index (IPI) score, B symptoms and *FCGR3A*-158 genotype. DNA sequencing of a 162 bp PCR product amplified specifically from the *FCGR3A* gene, determined genotype.[8]

There were 69 patients with indolent lymphoma (12 with International Working Formula (IWF) grade A, and 57 with grade B or C) and 125 patients with aggressive lymphoma (IWF grade D, E, F, G, H, I or J-known T-cell phenotypes were excluded). The IPI scores for all 194 patients were predictive of progression free and overall survival by Kaplan-Meier analysis as expected.

For the entire 194 patients, frequencies of the VV, VF, and FF polymorphisms, were 13%, 46% and 43% (see *Online Supplementary Table S1* for subgroup frequencies). The χ^2 test showed that there were no significant differences in the genotype frequencies (p=0.8752) between the two disease subgroups.

The population was in Hardy-Weinberg equilibrium. We calculated that our analysis had 89% power to detect differences attributed to genotype in 194 patients. We recognize that our cohort includes a somewhat heterogeneous group of indolent and aggressive NHL. A limitation of our analysis is that the power to detect small differences in outcomes in these smaller groups is reduced.