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with 0.07%, 0.29%, 0.01%, and 0.01%, respectively, in EBV-seropositive subjects (Figure 1A). Another important difference between our findings and those of the previous study is that the proportions of LCL-reactive cells in the γδ T-cell and NK-cell populations were 0.3% and 0.2%, respectively, in our study (Figure 1B), compared with 21.7% and 38.9%, respectively, in the previous study.[5]

Because a proportion of cells within LCLs are lytically infected, the T-cell response to LCLs comprises responses to both lytic and latent EBV antigens. In our study, the mean frequency of lytically infected cells in 11 LCLs was 2.1%, as determined by expression of the immediate early protein BZLF1 measured with the BZ1 mAb (Santa Cruz Biotechnology). This is higher than the 0.6% level of lytic infection found by the earlier study.[5] To reduce the possible effect of variability in the level of lytic infection on the T-cell response to LCLs, we used a PBMC/LCL ratio of 2:1, compared with 10:1 used in the previous study.[5] Varying the PBMC/LCL ratio from 2:1 to 10:1 did not alter the LCL-specific frequencies in the $CD4^+$ and $CD8^+$ T-cell populations, but increasing the ratio to 20:1 decreased the frequencies. The differences between our results and those of Bhaduri-McIntosh et al may be due to technical differences in the assays used, such as a shorter incubation time of 6 hours compared with 20 hours and a longer LCL culture time of 3 months compared with 3-4 weeks, respectively.[5] Our longer LCL culture time was used to avoid contamination of the LCL by EBV-specific T cells, which could falsely increase the recorded frequency of LCL-reactive cells in the tested populations. Furthermore, we studied nearly 4 times as many EBV-exposed subjects as the earlier study.[5]

Our finding that the frequency of EBV-specific T cells was much higher in the $CD8^+$ T-cell population than the $CD4^+$ T-cell population is consistent with previous studies using other assays.[6-8] Studies using the IFN-γ ELISPOT assay to measure the response to autologous LCLs in fractionated T-cell populations of immune subjects reported that the frequency of LCL-specific T cells was 5-7 times higher in the $CD8^+$ population than in the $CD4^+$ population.[6,7] Another study found that the frequency of $CD4^+$ T cells responding to EBV-infected B-cell lysates in healthy EBV carriers[8] was much lower than the frequency of $CD8^+$ T cells specific for EBV epitopes.[2] Our finding that LCL-reactive cells constituted 1.6% of the $CD8^+$ population in healthy immune subjects (Figure 1B) is similar to the 1.3% found by Yang et al using an IFN-γ ELISPOT assay.[6] The great preponderance of $CD8^+$ T cells over $CD4^+$ T cells in the immune response to EBV in healthy EBV carriers is consistent with the massive expansion of $CD8^+$ T cells, but not $CD4^+$ T cells, during infectious mononucleosis[9] and the role of EBV-specific $CD8^+$ T cells as the principal effectors mediating regression of LCL outgrowth in healthy EBV carriers.[10]

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Contribution: M.P.P. planned the study, helped analyze the results, and wrote the manuscript; P.A.C. performed the laboratory studies and analyzed the data; C.M.M.P. assisted with the laboratory studies; S.R.B. helped plan the study and analyze the data; and all authors read and approved the final manuscript.

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To the editor:

Significant weight gain in patients with chronic myeloid leukemia after imatinib therapy

Imatinib has had an impressive impact on the management of chronic myeloid leukemia (CML) patients, with the majority achieving durable complete cytogenetic responses, and, at present, tyrosine kinase inhibitor therapy is expected to be life-long. As a result of this dramatic change in the prognosis of CML, new clinical and scientific challenges are to be met and the clinical focus now includes the management of long-term side effects.

It is anticipated that most patients with newly diagnosed hematologic malignancies will experience weight loss before and during the initial course of treatment because of a multifactorial

Table 1. Weight gain in CML patients after imatinib therapy

Months after imatinib therapy	N	Median weight gain (kg)	% weight gain	P	No. of patients with weight gain
6	48	3.4 (−6.0, 11.0)	4.8 (−5.3, 14.2)	< .0001	37 (77%)
12	45	4.1 (−3.1, 17.9)	5.3 (−4.2, 22.9)	< .0001	38 (84%)
18	43	4.7 (−3.4, 17.9)	6.3 (−4.8, 23.0)	< .0001	36 (84%)
24	35	5.2 (−8.4, 21.7)	6.2 (−12.0, 27.1)	< .0001	30 (83%)

CML indicates chronic myeloid leukemia.

process. The impact of imatinib therapy on body habitus in newly diagnosed patients with CML has not been previously reported. We conducted a retrospective analysis on weight change in newly diagnosed patients with CML in chronic phase (CP) subsequently treated with imatinib. Fifty adult patients with CML (median age 47.6 years [25-78]; male [n = 29], female [n = 21]) in CP were consecutively treated with 400 mg daily of imatinib and their weight analyzed at 6 monthly intervals for a period of 24 months. Patients were excluded if additional co-morbidities that could influence weight loss or gain were present, such as thyroid disorders, diabetes, and clinical fluid retention. The median weight at the start of imatinib therapy was 76.8 kg (range 49.7-123). There was a statistically significant gain in weight in evaluable patients even at 6 months ($P < .0001$), with more than 75% of patients gaining weight (Tables 1 and 2). The median BMI at the start of imatinib therapy was 26.3 kg (18.3-47.5) Our data show that even with a high starting percentage of by definition, obese (BMI > 30) patients (20%), the percentage of obese patients more than doubles by 18 months after the start of imatinib treatment, and is statistically significant.

Obesity is associated with increased cancer incidence and mortality. Complex molecular links exist between obesity and metabolic dysfunction. Imatinib principally targets the tyrosine kinase activity of BCR-ABL1, in addition to inhibitory effects on KIT, ARG, and platelet-derived growth factor receptor (PDGFR) kinases. Obesity is recognized to be associated with macrophage accumulation and inflammation in adipose tissue and macrophage-secreted factors have been reported to inhibit the differentiation of preadipocytes into adipocytes.[1] Macrophage-conditioned medium has been found to stimulate PDGFR tyrosine phosphorylation, which can be inhibited by the addition of imatinib. Inhibition of PDGFR by imatinib has been found to disrupt the prosurvival effect on preadipocyte survival. PDGF is also strongly implicated in atherosclerosis and stimulates proteoglycan synthesis, however imatinib reduces low-density lipoprotein binding in vitro and aortic deposition in vivo.[2] Imatinib has also been variably reported to have a favorable effect on glucose metabolism in diabetic patients, possibly by affecting insulin signaling pathways,[3] protection against pancreatic cell death, and improved insulin sensitivity. Furthermore, imatinib has been reported to induce normalization of the levels of serum cholesterol, triglycerides as well as low- and high-density lipoproteins. Mast cell disorders can be responsive to imatinib and it is notable that mast cells have been recognized to contribute to diet-induced obesity and diabetes.[4]

Table 2. Changes in BMI in CML patients during therapy with imatinib

	Months after imatinib therapy				
BMI	0	6	12	18	24
Non-obese	36 (80%)	29 (68%)	27 (68%)	22 (56%)	19 (58%)
Obese	9 (20%)	14 (32%)	13 (32%)	17 (44%)	14 (42%)
P value comparison with time 0		.18	.19	.02	.03

BMI indicates body mass index.

Therefore, it is apparent that the observed increase in weight of several patients treated with imatinib may be secondary to a complex etiology. Further prospective investigations aimed at investigating the molecular mechanisms of this metabolic effect and its clinical impact is warranted.

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