Comment on "The negative impact of being underweight and weight loss on survival of children with acute lymphoblastic leukemia."

The accumulating evidence of a casual relationship between obesity and enhanced cancer risk has promoted us the introduction of a new term "adiponcosis", derived from the fusion of the words "adiposis" and "oncosis".[1] Increased incidence of hematologic tumors is strongly associated with obesity. However, it is unknown whether leukemia incidence is, for instance, directly increased by obesity or rather by other genetic or socio-economic factors or lifestyle. It has emerged that, across many populations, there is an association between acute lymphoblastic leukemia (ALL) risk and obesity, although it is still not known why this occurs. It was observed that obesity can directly accelerate the progression of ALL in mice; older obese mice had accelerated ALL onset and higher leptin, insulin, and IL-6 levels than controls, all obesity-related hormones with potential roles in leukemia pathogenesis.[2] Past observational studies had showed higher prevalence of overweight and obese individuals among adult survivors of ALL than among adults in the general population. More recently, studies were extended to childhood cancer survivors. In particular, following treatment for ALL, these patients tend to be less active and at greater risk for obesity than their healthy peers. This study, which assessed cases prospectively over a 12-month period during the early phases of treatment, extends prior reports by demonstrating that these outcomes are evident at an early stage in treatment.[3] Indeed, a pilot study demonstrated that home exercise intervention during ALL maintenance therapy is feasible and has promise for efficacy.[4] In an attempt to determine if weight gain, early in therapy, is predictive of obesity at the end of treatment, Withycombe *et al.*[5] suggested that monitoring weight trends during childhood ALL induction therapy may be useful in identifying which patients are at highest risk for obesity development so that early intervention strategies may be implemented. Furthermore, another study showed that obese or underweight patients at diagnosis and for 50% or more of the time between end of induction and start of maintenance therapy had inferior event-free survival (EFS). Normalization of weight during that period was related to a mitigation of this risk comparable to never being obese or underweight. Obese or underweight status at start of each treatment phase was significantly associated with specific patterns of treatment-related toxicity.[6] Of note, these authors very recently described the association between obesity and the key prognostic marker of minimal residual disease (MRD) in the bone marrow in pediatric B-precursor ALL. This study shows that obesity during induction was associated with both a significant greater risk for persistent MRD and with poorer EFS irrespective of end-induction MRD.[7] This is important since it links obesity also with leukemia relapse; however, the limitations of this study are due to a selected population (Hispanic children who are prone to obesity) and the fact that heterogeneity of drug induction therapy cannot be excluded. However, another recent work published on Haematologica, performed on a cohort of newly diagnosed Dutch pediatric patients with ALL, although confirming that underweight patients have a similar overall survival and event-free survival as compared to patients with normal weight or who are overweight, shows that patients who are underweight have an increased risk of relapse. In addition, this study further extends our knowledge since it demonstrates that patients with loss of body mass index during the first 32 weeks of treatment had a similar risk of relapse and event-free survival, but a decreased overall survival compared to patients without a loss of body mass index. Indeed, loss of body mass index during treatment seems to mainly consist of a loss of lean body mass.[8] These authors, in line with previous studies, agree on the importance of the physical exercise programs early during pediatric ALL treatment and suggest that pediatric ALL patients could benefit from interventions that enhance lean body mass in addition to the commonly used interventions. What comes out from the literature is that the 'extremes' concerning body weight status matter, and although the authors of this study were not able to associate obesity with survival, the comment should be made that outcome of overweight patients may be compromised due to a deficient immune response because of higher inflammation parameters, and that they have an increased risk of comorbidities related to being overweight.

It is currently believed that a positive correlation between obesity and cancer is driven by white adipose tissue. Adipocytes secrete factors that play roles in cancer cell proliferation, migration, and metastasis. SDF-1α secretion induces ALL cells to migrate into adipose tissue; however, the precise mechanisms whereby adipocytes may contribute to ALL relapse are still not known. Numerous epidemiological studies revealed that chronic inflammation, that is associated with enlarged body fat mass, predisposes to different types of tumors. In the microenvironment of most neoplastic tissues, an inflammatory component related with obesity is finely orchestrated by NF-κB and Stat3.[9] Anti-inflammatory effects have been proposed among other plausible biological mechanisms, as being the basis of the possible association between physical activity and hematologic cancers. However, there is still insufficient epidemiological evidence for this. In conclusion, the emerging studies strongly support the 'obesity-leukemia' link. Thus, the term "adiponcosis" can find an application also in hematologic tumors, and although the mechanisms of this connection remain largely unknown, we believe that the majority of people are unaware that obesity and overweight can increase also the risk of leukemia. The molecular mechanisms at the basis of the obesity-cancer link[10] must be explored in order to provide new ways of prevention and treatment.

Maurizio Bifulco, and Anna Maria Malfitano

Department of Medicine and Surgery, University of Salerno, Via Allende, Baronissi, Salerno, Italy and Department of Pharmacy, University of Salerno, Via Giovanni Paolo II, Fisciano, Salerno, Italy

Correspondence: mbifulco@unisa.it/amalfitano@unisa.it

doi:10.3324/haematol.2014.122168

Key words: acute lymphoblastic leukemia, adiponcosis.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Bifulco M., Pisanti S. "Adiponcosis": a new term to name the obesity and cancer link. J Clin Endocrinol Metab. 2013;98(12):4664–4665.
2. Yun JP, Behan JW, Heisterkamp N, et al. Diet-induced obesity accelerates acute lymphoblastic leukemia progression in two murine models. Cancer Prev Res (Phila). 2010;3(10):1259-1264.
3. Fuemmeler BF, Pendzich MK, Clark K, et al. Diet, physical activity, and body composition changes during the first year of treatment for childhood acute leukemia and lymphoma J Pediatr Hematol Oncol. 2013;35(6):437–443.

4. Esbenshade AJ, Friedman DL, Smith WA, et al. Feasibility and initial effectiveness of home exercise during maintenance therapy for childhood acute lymphoblastic leukemia. Pediatr Phys Ther. 2014; 26(3):301-307.
5. Withycombe JS1, Smith LM, Meza JL, et al. Weight change during childhood acute lymphoblastic leukemia induction therapy predicts obesity: A report from the Children's Oncology Group. Pediatr Blood Cancer. 2014; Nov 18.
6. Orgel E, Sposto R, Malvar J, et al. Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: A report from the Children's Oncology Group. J Clin Oncol. 2014;32(13):1331-1337.
7. Orgel E, Tucci J, Alhushki W, et al. Obesity is associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia. Blood. 2014;124(26):3932-3938.
8. den Hoed MA, Pluijm SM, de Groot-Kruseman HA, et al. The negative impact of underweight and weight loss on survival of children with acute lymphoblastic leukemia. Haematologica. 2015;100(1):62-69.
9. Mantovani A. Molecular pathways linking inflammation and cancer. Curr Mol Med. 2010;10(4):369-373.
10. Bifulco M. The Obesity and Cancer link. Ann Oncol. 2014; Nov 18.