SUPPLEMENTARY DATA

METHODS

Patients' selection:

This study was designed to describe the prevalence of symptomatic ON, to identify risk factors for this side effect and to evaluate its impact on quality of life. For this purpose, we analyzed all patients included during the years 2004-2009 in the French L.E.A. cohort. L.E.A. (for "Leucémie de l'Enfant et de l'Adolescent") is a multicenter late effect program initiated in 2003 to evaluate prospectively long-term health status of childhood leukemia survivors who had been treated after 1980. Details of the whole program have been previously described.[14] Briefly, data are collected during specific medical visits at predefined dates, beginning one year after completion of chemotherapy or one year after HSCT, then repeatedly every 2 years until the patient reaches 20 years of age and has a more than 10 years follow-up duration from diagnosis, and every 4 years thereafter. All patients (or their parents or legal guardians) have signed informed consent. The study was approved by the French National Program for Clinical Research, the French National Cancer Institute (InCA) and an ethics committee.

Study endpoint:

ON was one of the late side effects that were systematically evaluated in the LEA program. During the medical visits, each patient with a previous diagnosis of symptomatic ON was identified. Date of diagnosis, joints involved and treatments were detailed. Patients without such a history were clinically evaluated during the medical visit and MRI of the symptomatic joints was proposed if ON was clinically suspected.

Steroid therapy:

Cumulative steroid doses differed according to the protocol used for leukemia treatment. For each patient, we collected the cumulative dose of prednisone and dexamethasone received as part of conventional therapy and during the post-transplantation period. With these data, the total steroid dose in equivalent of prednisone received by each patient was calculated using the formula: total steroid dose in mg/m² = dose of prednisone + (dose of dexamethasone x 6.67), as previously described.[15-17] For practical reasons, short courses of steroid therapy given as antiemetic or for drug intolerance were not taken in consideration.

Quality of Life (QoL):

The QoL of adult patients was assessed using the SF-36 questionnaire[18], a reliable instrument in assessing self-perceived health status in adult survivors of childhood cancer.[19] Its French version is well validated. The SF-36 is comprised of 36 items describing 8 dimensions: physical functioning (PF), social functioning (SF), role limitations due to physical health problems (RP), role limitations due to emotional problems (RE), general mental health (MH), vitality (VT), bodily pain (BP) and general health perceptions (GH). Additionally, two summary composite scores are generated: the physical composite score (PCS) and the mental composite score (MCS). The PCS and MCS scores are norm-based, using a linear T-score transformation with a mean of 50. The SF-36 yield scores on a 0–100 scale, where 0 represents the lowest QoL and 100 the highest.

Statistical methods:

Binary variables were summarised using counts and percentages and continuous variables with means and standard error of mean (s.e.m.). χ^2 and Fischer's exact test were used to compare qualitative variables. Quantitative variables were compared using the Student test or the Mann-Whitney test. Prevalence rates of ON were expressed as percentage of affected patients in a given population. Cumulative incidences of ON over time were estimated using the Kaplan-Meier method, displayed with their 95% confidence interval (CI) and compared with the log rank test. Multivariate logistic regression analyses were used to construct models of association between prevalence rates of ON and potential risk factors. Odds ratios (OR) were reported with their 95% CI. Multiple linear regression models were constructed to explore the potential link between occurrence of ON and the patient's long-term QoL scores. Each model is presented with its standardised β-coefficient, measuring the strength of osteonecrosis effect on the QoL dimension's score. To help interpret the clinical significance of differences in QoL dimensions' mean scores, effect sizes were calculated by dividing the difference between the mean score of patients with ON and the mean score of patients without ON by the standard deviation of the non-ON group. We considered an effect size of 0.2-0.49 as "small", 0.5-0.79 as "medium" and 0.8 or higher as "large".[20] All tests were two-sided. Statistical significance was defined as $p<0.05$. The statistical analyses were performed using the PASW Statistics software version 17.0.2.