

Treatment of T Cell Lymphoblastic Lymphoma in Children and Adolescents: Israel Society of Pediatric Hematology Oncology Retrospective Study

Ofrat Beyar Katz¹, Ayelet Ben Barak MD¹, Gali Abrahami MD³, Nira Arad MD¹, Yoav Burstein MD⁴, Rina Dvir MD⁴, Salvador Fischer MD³, Joseph Kapelushnik MD⁵, Haim Kaplinsky MD⁶, Amos Toren MD PhD⁶, Shoshana Vilch-Revel MD⁶, Michael Weintraub MD⁷, Isaac Yaniv MD³, Shai Linn MD PhD², Boris Futerman MSc² and Myriam Weyl Ben-Arush MD¹

¹Department of Pediatric Hematology-Oncology and ²Epidemiology Unit, Meyer Children's Hospital, Rambam Health Care Campus affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

³Department of Pediatric Hematology-Oncology, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

⁴Pediatric Hematology-Oncology Unit, Dana Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

⁵Department of Pediatric Hematology-Oncology, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

⁶Department of Pediatric Hematology-Oncology, Safra Children's Hospital, Sheba Medical Center affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

⁷Department of Pediatric Hematology-Oncology, Hadassah University Hospital and Hebrew University Hadassah Medical School, Jerusalem, Israel

ABSTRACT: **Background:** Survival in T cell lymphoblastic lymphoma has improved over the past 30 years, largely due to treatment protocols derived from regimens designed for children with acute lymphoblastic leukemia.

Objectives: To assess the outcome of the NHL-BFM-95 protocol in children and adolescents hospitalized during the period 1999–2006.

Methods: We conducted a retrospective multi-institutional, non-randomized study of children and adolescents up to age 21 with T cell lymphoma admitted to pediatric departments in six hospitals in Israel, with regard to prevalence, clinical characteristics, pathological characteristics, prognostic factors, overall survival (OS) and event-free survival (EFS). All patients had a minimal follow-up of one year after diagnosis. The study was based on the NHL-BFM-95 protocol.

Results: At a median follow-up of 4 years (range 1–9 years), OS and EFS for all patients was 86.5% and 83.8%, respectively. OS was 86.7% and 83.3% for patients with stage III and stage IV, respectively, and EFS was 83.3% and 83.3%, respectively. EFS was 62.5% for Arab patients and 89.7% for Jewish patients ($P = 0.014$). Patients who did not express CD45 antigen showed superior survival ($P = 0.028$). Five patients (13.5%) relapsed, four of whom died of their disease. Death as a consequence of therapy toxicity was documented in one patient while on the re-induction protocol (protocol IIA).

Conclusions: Our study shows that OS and EFS for all patients was 86.5% and 83.8%, respectively.

IMAJ 2011; 13: 161–165

KEY WORDS: children, adolescents, chemotherapy, lymphoblastic lymphoma, T cell

Non-Hodgkin lymphoma accounts for 6% of all malignancies in children in developed countries. Lymphoblastic lymphoma, mostly from T cell lineage, accounts for 30% of cases, and about 90% of children suffering from lymphoblastic lymphoma are diagnosed with T cell lymphoblastic lymphoma. Survival in T-LBL has improved over the past 30 years, largely due to treatment protocols derived from regimens designed for children with acute lymphoblastic leukemia [1,2]. Between 1983 and 1991, Link et al. [3] reported successful results in patients with early-stage NHL who were treated with a short course of chemotherapy of lessened intensity without irradiation of the primary sites of involvement and without continuation of therapy. The one subtype that was exceptional was lymphoblastic lymphoma, due to the inferior event-free survival compared with other subtypes and its beneficial response to continuation therapy [3].

Mora and co-researchers [4] reported their experience with lymphoblastic lymphoma in children treated according to the LSA2-L2 protocol during the years 1971–1990. This 10-drug combination produced prolonged significant results: overall survival of patients was 79% and overall event-free survival was 75%. The authors concluded that chemotherapy alone appeared to be a sufficient prophylaxis against central nervous system recurrence. In 2000, the European group, BFM (Berlin-Frankfurt-Munster), showed that with intensive chemotherapy similar to the treatment approach for acute lymphoblastic leukemia and an efficacious CNS prevention, favorable EFS in the range of 90% could be achieved in childhood T-LBL [5].

The aim of the next BFM protocol, NHL-BFM-95, was to omit CNS and local radiotherapy, tailoring treatment accord-

NHL = non-Hodgkin lymphoma
BFM = Berlin-Frankfurt-Munster
OS = overall survival

T-LBL = T cell lymphoblastic lymphoma
CNS = central nervous system
EFS = event-free survival

ing to the response to induction chemotherapy. In most of the studies, no clinical or immunophenotype features succeeded in identifying a subgroup of patients with a significantly increased risk of treatment failure. In addition, no epidemiological prognostic factors were reported in the literature. The aim of our study was to report the results of a retrospective, non-randomized study in children and adolescents with T-LBL treated in the main pediatric hematology oncology departments in Israel based on the NHL-BFM-95 protocol.

PATIENTS AND METHODS

Children and adolescents with T-LBL and under 21 years of age were eligible for this NHL-BFM-95 study. Patients with B cell lymphoblastic lymphoma were excluded, as were patients with immunodeficiency, human immunodeficiency virus infection, prior solid organ transplant and previous malignancy and/or chemotherapy. From January 1999 through December 2006, 37 patients from six pediatric oncology centers in Israel were enrolled. All patients received treatment based on the NHL-BFM protocol.

DEFINITIONS

The diagnosis of T-LBL was made by tissue biopsy of lymph node or tumor mass. Immunological classification was performed according to the criteria of the European Group for immunophenotyping of leukemia. Histopathological classification was made according to the World Health Organization classification for hematological malignancies. Assessment of the staging of the disease was made by laboratory studies, such as peripheral smear, aspiration of bone marrow, cerebrospinal fluid, serum lactate dehydrogenase, and imaging studies such as ultrasound, X-ray, computed tomography, positron emission tomography or gallium scan. T-LBL patients were staged as I-IV according to the St. Jude staging system. Bone marrow involvement was diagnosed if there were > 5% and < 25% lymphoblasts in the bone marrow. If there were more than 25% lymphoblasts, a diagnosis of acute lymphoblastic leukemia was made. CNS involvement was diagnosed based on one of the following criteria:

- More than five cells in the CSF and identifiable blasts in the CSF
- Cerebral/medullary infiltrates on cranial/spinal MRI
- Cranial nerve palsy that could not be explained by extradural lesions.

TREATMENT

The therapy regimen was based on the NHL-BFM-95 protocol, without prophylactic cranial and local irradiation. Patients were divided into two subgroups depending on their staging grade in order to adjust the specific treatment. All stages received induction therapy followed by M protocol and maintenance.

Stages III+IV received, in addition, a re-induction protocol. Cranial irradiation was performed only on patients with initial CNS disease. CNS-positive patients received cranial irradiation in age-dependent doses. Children less than 1 year of age did not receive cranial irradiation, those between the ages of 1 and 2 years received 12 Gy, and children over 2 years old received 18 Gy. Response to treatment was observed on day 33 from initiation of therapy and at the end of the induction. For patients diagnosed with a mediastinal mass, complete disappearance of the mass on X-ray on day 33 was considered a full response to treatment. In cases of a residual mass on X-ray, a CT was performed to assess the volume of the mass. Patients with regression of more than 70% of the mass on day 33 of treatment and/or less than 5% blasts in the bone marrow and no blasts in the CNS continued therapy as planned. Patients with less than 70% of mass regression on day 33 of treatment and/or more than 5% blasts in the bone marrow and blasts in the CNS were treated with the acute lymphoblastic leukemia-high risk therapy. Treatment of a relapse was based on various second-line chemotherapy courses and allogeneic bone marrow transplantation.

STATISTICAL ANALYSIS

Patients were identified in the data bank of the Israel Society of Pediatric Hematology Oncology, the appropriate files were received from the medical centers, and the details were transmitted to a questionnaire. The data were transferred to a statistical software package (SPSS 15) and checked for perfection and adjustment. Analysis of EFS was performed using the Kaplan-Meier method with differences compared by the log-rank test. Differences in the distribution of individual parameters among patient subsets were analyzed using the chi-square test or Fisher exact test. EFS was determined from the time of diagnosis until the first event of death, second malignancy or relapse. Overall survival was determined from the time of diagnosis until the patient's death. Toxicity of therapy was determined by WHO grading.

RESULTS

PATIENT CHARACTERISTICS [TABLE 1]

Of the 37 evaluated patients, 31 were boys and 6 were girls. Median age was 9 years (range 2-19 years). With regard to ethnic origin 29 patients were Jewish and 8 were Arab. Twenty-six patients lived in a city and 11 lived in peripheral areas. Familial consanguinity was documented in three patients, none of whom had a history of malignancy, immune deficiency or chromosomal abnormality. No patient was diagnosed as stage I, one patient was diagnosed as stage II, 30 as stage III, and 6 as stage IV. Thirty-four (91.9%) patients had a mediastinal mass, 4 (10.8%) had bone marrow involvement, and 2 (5.4%) had CNS involvement, expressed by cranial nerve palsy of the

Table 1. Patient characteristics (n=37)

	No. of patients (%)
Gender	
Male	31 (83.8)
Female	6 (16.2)
Age (yrs)	
Range	2–19
Median	9
Ethnic origin	
Jewish	29 (78.4)
Arab	8 (21.6)
Primary site	
Mediastinum	34 (91.9)
Peripheral lymph nodes	2 (5.4)
Abdomen	1 (2.7)
Stage	
I	0
II	1 (2.7)
III	30 (81.1)
IV	6 (16.2)
LDH at presentation (U/L)	
< 500	10 (27)
> 500	27 (75)
Bone marrow involvement alone	4 (10.8)
CNS involvement alone	2 (5.4)
BM and CNS involvement	0

abducens nerve and facial nerve. Nine patients were diagnosed in a severe general condition that required mechanical ventilation. No patient had combined involvement of bone marrow and CNS or testicular involvement.

On laboratory examination the median value of LDH at diagnosis was 1000 U/L (range 226–9919 U/L) and of uric acid 4.5 mg/dl (range 1.7–47 mg/dl). Immunophenotype distribution showed that 40% expressed CD7 antigen, 35% expressed CD5 antigen, 29% expressed CD8 antigen, 24% expressed CD2 antigen and 11% expressed CD45 antigen.

RESPONSE TO TREATMENT ON DAY 33

Thirty-six patients showed regression of more than 70% of the tumor mass on day 33 and one patient had regression of less than 70%. For this patient, the therapeutic protocol was continued. After protocol M, re-induction was delivered, followed by surgical resection of the residual mediastinal mass (15 cm). Histology of the mass was not conclusive and an additional course of chemotherapy protocol III was added before maintenance. Follow-up of 2 years from the end of therapy did not show relapse of disease.

TREATMENT OUTCOME [FIGURES 1A-1D]

At a median follow-up of 4 years (range 1–9 years), OS and EFS for all patients was 86.5% and 83.8%, respectively. EFS was 83.3% and 83.3% for patients with stage III and stage

IV, respectively. OS was 86.7% and 83.3% for patients with stage III and stage IV, respectively. EFS for Arab patients was 62.5% and for Jewish patients 89.7% ($P = 0.014$). OS for Arab patients was 75% and for Jewish patients 89.7%.

PROGNOSTIC FACTORS

We searched for a clinical or immunophenotypic characteristic that would predict treatment failure and found that Arab ethnic origin accounted for inferior survival ($P = 0.014$) and that patients who did not express CD45 antigen showed superior survival ($P = 0.028$). No connection was shown between survival and other parameters such as gender, age and residency. In addition, we looked for a laboratory marker that would assist in tracking the efficacy of therapy. Although LDH at diagnosis was not associated with survival, we did see a gradual decline in LDH levels in the patients who survived.

RELAPSE

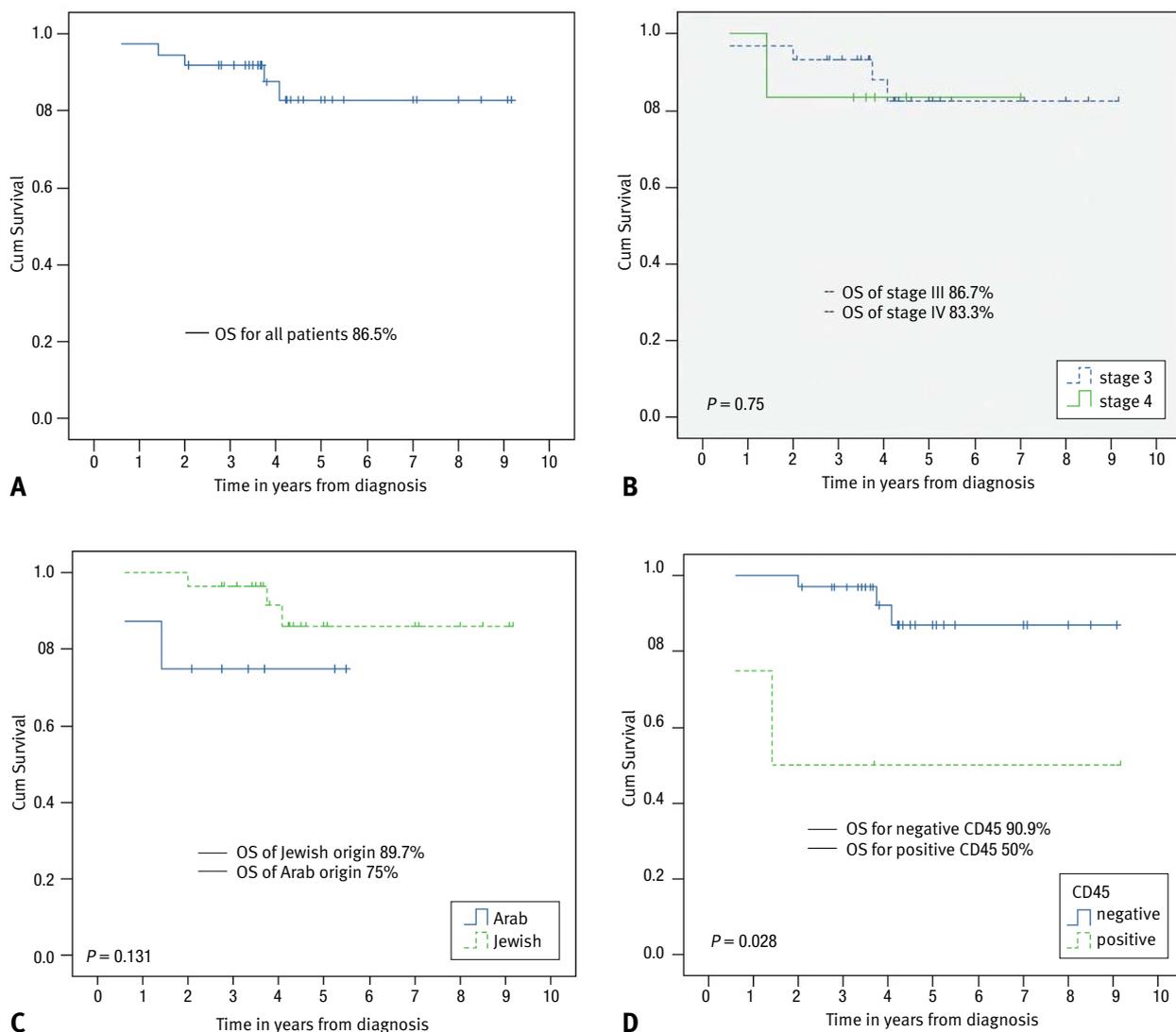
Five (13.5%) patients relapsed, four of whom died of disease. A relapse less than one year from diagnosis occurred in one patient, the only one who survived the relapse. The other four relapses were diagnosed after one year and up to 3.5 years from diagnosis, and none of these patients survived. Three patients had bone marrow relapse, one patient had local tumor failure, and one had CNS tumor failure (with no primary CNS involvement).

TOXICITY OF THERAPY

Death as a consequence of toxicity of therapy was documented in one patient during the re-induction protocol (protocol IIA). The patient was homozygous to APCR (activated protein C resistance) and MTHFR (methylene tetrahydrofolate reductase) and developed acute respiratory failure with fever and severe bone marrow aplasia; during his hospitalization he developed a pulmonary hemorrhage and died due to respiratory failure. No secondary malignancy was documented in any patient at a median follow-up of 4 years (range 1–9 years).

- Renal toxicity: There was no documentation of renal toxicity.
- Neurological toxicity: In protocol I, one patient developed tonic-clonic seizures. In protocol M, one patient developed neurological symptoms.
- Thrombotic toxicity: In protocol I, one patient developed sinus vein thrombosis. In protocol M, one patient who was known to have thrombophilia had a transient ischemic attack.
- Infections: In protocol I, one patient developed *Staphylococcus* coagulase-negative infection in a central line. In protocol M, one patient developed septic shock with negative blood cultures but had a rapid recovery after ablation of the central line. In protocol II, one patient developed

LDH = lactate dehydrogenase
OS = overall survival

Figure 1. Overall survival: **[A]** for all patients (n=37), **[B]** according to stage, **[C]** according to ethnic origin, and **[D]** according to immunophenotype

Staphylococcus coagulase-negative infection in the central line. On maintenance, one patient had herpes zoster.

- Gastrointestinal toxicity: In protocol I, one patient was diagnosed with acute pancreatitis and pancreatic pseudo-cysts without severe complications; asparaginase was stopped.

DISCUSSION

This report presents the results of a retrospective multi-institutional non-randomized study on a series of 37 patients with T lymphoblastic lymphoma treated with the NHL-BFM-95 protocol between 1999 and 2006. The Berlin-Frankfurt-Munster NHL-90 protocol for pediatric T-LBL showed that a leukemia-based protocol and prophylactic CNS radiotherapy

provided a 90% EFS [5]. The protocol was designed according to treatment response at induction therapy, without local irradiation. The aim of the next BFM-95 study was designed to omit CNS radiation prophylaxis even in advanced disease. Preventive CNS therapy was based on steroids, intrathecal and high-dose methotrexate.

We used the BFM-NHL-95 protocol and did not see more CNS recurrences than in previous BFM trials. The results obtained for all our patients showed OS and EFS of 86.5% and 83.8%, respectively. Mora et al. [4] reported their experience with lymphoblastic lymphoma in children treated according to the LSA2-L2 protocol and showed an OS of 79% and an overall EFS of 75% at a median follow-up of 20 years. Their protocol included chemotherapy and radiotherapy

to bulky disease; all cases of recurrence occurred within 4 years from diagnosis, and no significant prognostic factors were observed except stage of the disease [5]. Pillon and collaborators [6] reported their experience in 55 children with T-LBL treated according to the modified LSA2-L2 protocol (LNH-92) during the period 1992–1997. Overall survival was 72% and overall EFS 69%. They concluded that the outcome was inferior to recent trials that included re-induction treatment or a higher intensity therapy for high-stage disease. Treatment results of the EORTC CLG that included 119 patients with T-LBL treated with the BFM protocol without the use of cranial irradiation or local radiation showed an EFS of 77.5% and an OS of 86% [7]. In our study, the patients who achieved good response to prednisone after the first day of treatment had a better outcome (6 years, 100% vs. 14%). The Israel Society of Pediatric Hematology Oncology group experience showed that children and adolescents treated according to the BFM NHL-95 had a high EFS and OS; the therapeutic protocol was being used correctly and stood up to other international therapy results.

Regarding ethnicity, we found that the EFS for Arab patients was 62.5% and for Jewish patients 89.7% ($P = 0.014$). This finding is supported by the Israel Society of Pediatric Hematology Oncology experience in children with Burkitt lymphoma, showing an OS of 79.2% for Arab patients and 95.3% for Jewish patients ($P = 0.001$) [8]. No significant prognostic factors were observed between the two groups in this study, such as compliance difference or stage of disease at diagnosis, which would have raised the question of a genetic influence.

In our study we tried to locate an efficient marker that would assess response to treatment. We found that patients who did not express CD45 antigen showed superior survival ($P = 0.028$). According to the literature, expression of CD45 is not correlated with prognosis in T-LBL. In acute lymphoblastic leukemia, the identification of minimal residual disease is based on molecular biology testing such as FISH (fluorescent in situ hybridization) and PCR (polymerase chain reaction), as opposed to lymphoblastic lymphoma patients where a quantifiable parameter of response to treatment is lacking and most of the parameters are based on qualitative evaluation of the disease. In the current BFM protocol, response to treatment is observed by the disappearance of the mass on X-ray; in cases of a residual mass on X-ray a CT is performed to assess the volume of the mass. The Children's Oncology Group and the St Jude Children's Research Hospital searched for submicroscopic systemic disease and its clinical signifi-

cance by using a flow cytometric method that can detect one T-LBL cell among 10,000 normal cells from bone marrow and peripheral blood samples [9]. The EFS was 68.1% for patients with 1% T-LBL cells in bone marrow versus 90.7% for those with lower levels of marrow involvement. They concluded that measurements of disease dissemination at diagnosis might provide useful prognostic information.

In conclusion, our retrospective study of children and adolescents with T-LBL showed similar results to other international studies. However, there is a need for comparing the epidemiological results between Israel and other countries in the Middle East, Europe, and the United States. Randomized trials are warranted to define the characteristics of microscopic disease, to detect minimal residual disease, and to monitor response to therapy.

Corresponding author:

Dr. M. Weyl Ben-Arush

Dept. of Pediatric Hematology-Oncology, Meyer Children's Hospital, P.O. Box 9602, Haifa 31096, Israel

Phone: (972-4) 854-2502

Fax: (972-4) 854-2007

email: m_benarush@rambam.health.gov.il

References

1. Reiter A, Schrappe M, Parwaresch R, et al. Non-Hodgkin's lymphomas of childhood and adolescence: results of a treatment stratified for biologic subtypes and stage – a report of the Berlin-Frankfurt-Münster Group. *J Clin Oncol* 1995; 13: 359-72.
2. Tubergen DG, Krailo MD, Meadows AT, et al. Comparison of treatment regimens for pediatric lymphoblastic non-Hodgkin's lymphoma: a Childrens Cancer Group study. *J Clin Oncol* 1995; 13: 1368-76.
3. Link MP, Shuster JJ, Donaldson SS, Berard CW, Murphy SB. Treatment of children and young adults with early-stage non-Hodgkin's lymphoma. *N Engl J Med* 1997; 337: 1259-66.
4. Mora J, Filippa DA, Qin J, Wollner N. Lymphoblastic lymphoma of childhood and the LSA2-L2 protocol: the 30-year experience at Memorial-Sloan-Kettering Cancer Center. *Cancer* 2003; 98: 1283-91.
5. Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM group report. *Blood* 2000; 95: 416-21.
6. Pillon M, Pigiione M, Garaventa A, et al. Long-term results of AIEOP LNH-92 protocol for the treatment of pediatric lymphoblastic lymphoma: a report of the Italian Association of Pediatric Hematology and Oncology. *Pediatr Blood Cancer* 2009; 53: 953-9.
7. Uyttebroeck A, Suciu S, Laureys G, et al. Treatment of childhood T-cell lymphoblastic lymphoma according to the strategy for acute lymphoblastic leukaemia, without radiotherapy: long term results of the EORTC CLG 58881 trial. *Eur J Cancer* 2008; 44: 840-6.
8. Eldar AH, Futerman B, Abrahami G, et al. Burkitt lymphoma in children: the Israeli experience. *J Pediatr Hematol Oncol* 2009; 31: 428-36.
9. Coustan-Smith E, Sandlund JT, Perkins SL, et al. Minimal disseminated disease in childhood T-cell lymphoblastic lymphoma: a report from the children's oncology group. *J Clin Oncol* 2009; 27: 3533-9.

“It is impossible to enjoy idling thoroughly unless one has plenty of work to do. There is no fun in doing nothing when you have nothing to do. Wasting time is merely an occupation then, and a most exhausting one. Idleness, like kisses, to be sweet must be stolen”

Jerome K. Jerome (1859-1927), English writer and humorist, best known for the amusing travelogue *Three Men in a Boat*