CHAPTER 4

Quality of Life in Very Long-Term Survivors of Pediatric Lymphoid Malignancies: Effects of Intrathecal Chemotherapy and Cranial Irradiation

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Submitted
Abstract

Objective: Cranial radiation therapy (CRT) used to be part of standard treatment protocols for childhood lymphoid malignancies. In the Netherlands and Belgium, it was abolished around 1983 because of the detrimental side effects and replaced with more intense chemotherapy (CT). The very long-term effects on health-related quality of life (QoL) in cohorts diagnosed before and after this change - more than two decades after treatment – have not been compared with each other before. Moreover, little is known about effects on QoL this long after treatment, in middle adulthood.

Methods: Self-reports of physical health, mood states, physical and mental fatigue, cognitive failures, employment status, and educational attainment were acquired from a CRT-treated group (N = 38) 26 years post-diagnosis, and a CT-treated group (N = 43) 22 years post-diagnosis. These groups were compared with each other, but also with a control group (N = 47).

Results: The CT-treated group reported significantly more mental fatigue than controls, whereas the CRT-treated group reported significantly worse outcomes on physical functioning, role limitations due to physical health, energy/fatigue, general health, physical fatigue, mental fatigue, and educational level. Compared with the CRT-treated group, the CT-treated group reported significantly higher levels of physical functioning, less role limitations due to physical health, and higher educational attainment. Higher doses of CRT and female gender were confirmed as risk factors.

Conclusion: CRT-treated survivors reported reduced health-related QoL in multiple domains, whereas the CT-treated group only reported heightened levels in one domain. Overall, the results indicate that the abolishment of CRT has ensured a
higher standard of QoL for very long-term survivors of childhood lymphoid malignancies.
Introduction

Thanks to substantial improvement of treatment, survival rates of children suffering from pediatric lymphoid malignancies such as acute lymphoblastic leukemia (ALL) are currently approximately 90%.\textsuperscript{1} The increase in survival rate raises questions as to whether long-term, high quality of life (QoL) standards can be ensured for ALL survivors, as late effects of treatment pose a threat to QoL. Current ALL treatment protocols involve systemic combination chemotherapy (CT) and additionally, prophylactic intrathecal chemotherapy, aimed at reaching cancer cells hiding in the meningeal space that could cause a relapse.\textsuperscript{2} Cranial radiation therapy (CRT) used to be included in the standard treatment protocols as central nervous system (CNS)-prophylaxis. However, CRT is associated with significant neurotoxic effects and severe late sequelae. Some of the physical morbidities observed in adult survivors of ALL treated with CRT include impaired growth, decreased fertility, cardiopulmonary, endocrine, and musculoskeletal disorders, a compromised immune system, as well as recurrent or secondary cancers.\textsuperscript{3-6} It is conceivable that these morbidities can negatively affect QoL. Decreased QoL, among which depressive psychological thoughts, have been commonly reported among leukemia survivors compared to siblings.\textsuperscript{7-10}

Current regimens deploying CT only are still intensive and toxic and children treated for leukemia are still at risk for developing long-term chronic health conditions.\textsuperscript{11,12} Essig et al. (2014) investigated the risk of late effects in children diagnosed with ALL. They examined data from the Childhood Cancer Survivor Study at a median follow-up time of 18 years. Compared to 32% of siblings, 47% of survivors reported more than one chronic health disorder, and 16% reported a severe or life-threatening disorder (compared to 9% of siblings).\textsuperscript{12} Krull et al. (2013) also associated CNS-directed CT with reduced health-related (HR) QoL.\textsuperscript{13} Despite these outcomes, omitting CRT has likely improved the overall QoL for long-term
survivors of ALL. The current study will evaluate this effect by directly comparing two Dutch-speaking cohorts, one treated with CRT and one without, on average 22-26 years after diagnosis, controlling for age at assessment (AaA), age at diagnosis (AaD), and gender. For each group, the effects of these factors will be analyzed as well, in addition to effects of treatment intensity.

Effects on QoL this long after diagnosis have been studied rarely. However, late effects in adult survivors might differ greatly from those experienced by children and teens. Furthermore, childhood cancer survivors with a follow-up of 20 years or longer have reported significantly lower HR QoL than those with a follow-up shorter than 20 years after diagnosis. Blaauwbroek et al. (2007) described that the experience of late effects changes with the course of time since diagnosis, and that new issues, such as worries about fertility, job discrimination, or lower rates of marriage, may arise as cancer survivors approach and enter adulthood. Similarly, perceived physical and mental wellbeing might change. Therefore, we used the RAND-36 to assess our CT-treated and CRT-treated cohorts, and a group of controls consisting of siblings, spouses and friends of the survivors, and additionally used self-report measures of mood states, mental and physical fatigue, cognitive failures, academic achievement and employment status.

**Methods**

**Participants**

QoL questionnaire data were analyzed of 43 CT-treated survivors, 38 CRT-treated survivors and 47 controls. The questionnaires were completed at home, after the participants had received them at an appointment for neuropsychological assessment, and sent back by mail. Seventy-five percent of the people who participated in the neuropsychological assessments also completed the questionnaires.
The cohort was identified from records of the VU University Medical Center, the Academic Medical Center Amsterdam (The Netherlands) and the University Hospitals Leuven (Belgium). The ethical principles of the Helsinki Declaration were followed and approval was obtained from the ethical committees of all participating centers. Survivors were considered eligible if they were diagnosed after 1978 and at least 18 years post-diagnosis. All participants were asked about use of psychotropic medication, neurological or psychiatric diagnoses, pregnancy, and color-blindness. They also needed to master the Dutch language. A flow-chart of patient exclusion is shown in Figure 1. The inclusion distribution across different risk groups gave no reason to suspect response bias. Participating survivors were asked to bring along a sibling, spouse or close friend as a control who also filled out the QoL questionnaires.

Chemotherapy intensity varied according to classification of the disease in standard-risk or high-risk for relapse. In the current study, 27 standard-risk CT-treated patients were included. They were treated according to the Dutch Childhood Leukemia Study Group (DCLSG) protocol ALL-6, which consisted of 13 intrathecal (IT) injections of 12 mg methotrexate (MTX) and intravenous (IV) injections of 3 x 2 g/m² MTX, or the European Organization for Research and Treatment of Cancer (EORTC) Trial 58831 (6 x 12 mg MTX IT and 2 g/m² MTX IV). Furthermore, 16 high-risk CT-treated patients were included in this study. They were treated with customized protocols based on either EORTC Trial 58832 (8 x 12 mg MTX IT and 10 g/m² MTX IV), the BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone) protocol (customized dose of MTX IV), or ALL-6 (customized additional MTX IV) without CRT.
Figure 1. Flow-chart of patient inclusion
Furthermore, 22 standard-risk CRT-treated survivors, five high-risk CRT-treated survivors, and 11 survivors treated for relapse were included. These survivors were treated according to Berlin-Frankfurt-Münster (BFM)-based protocols\(^{19}\). Between 1979 and 1983, standard-risk patients were treated according to Dutch Childhood Leukemia Study Group (DCLSG) protocol ALL-5 or the Riehm protocol, both characterized by CRT (15–25 Gy) and 5-7 IT injections of 12-12.5 mg of MTX, without the use of leucovorin. High-risk patients from this period were treated with additional customized intravenous (IV) high-dose MTX. Administration of MTX IV was always followed by leucovorin (12–15 mg/m\(^2\) every 6 hr until serum levels of MTX had dropped below 10–7 mol/L). Group means of cumulative doses were calculated excluding missing data. Doses of CRT were available for all patients, but doses of MTX IV were missing for three survivors. As CT doses varied greatly in the high-risk groups, dose was analyzed as a continuous variable instead of two risk categories.

**Measurements of HR QoL**

The **RAND 36-Item Health Survey** is a self-report measure tapping on eight health scales (n items) with reference to the past four weeks: physical functioning (10), bodily pain (2), role limitations due to physical problems (4), role limitations due to personal or emotional problems (3), emotional well-being (5), social functioning (2), energy/fatigue (4), and general health perceptions (5).\(^{20,21}\) Raw item scores are recoded into values on a 100-point scale. Items belonging to the same scale are averaged. A high score represents a more favorable health evaluation. Internal consistency, validity, and test-retest reliability are sufficient.\(^{21,22}\)

The **Profile of Mood States (POMS)** is a measure of psychological distress.\(^{23}\) Here, a shortened version of the Dutch POMS was used.\(^{24}\) This 32-item version consists of five subscales (n items): Depression (8), Anger (7), Fatigue (6), Vigor (5), and Tension (6). On a 5-point Likert scale, respondents indicate the degree to which each item described them with reference to the last week. Higher scores indicate
higher levels of the affective states. Psychometric properties of the Dutch translation of the POMS were investigated and approved.24,25

The Multidimensional Fatigue Inventory (MFI-20) is a 20-item self-report instrument designed to measure fatigue in cancer patients.26 It consists of five subscales (4 items each): general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. On a 7-point scale, respondents indicate to what extent a particular statement applied to them at that moment. Higher scores represent higher levels of fatigue. Internal consistency and validity were approved.26,27

The Cognitive Failure Questionnaire (CFQ) assesses the frequency of experienced failures in perception, memory, and motor function in everyday life28. We used the Dutch translation of the CFQ29,30, which can be administered both to patients with cognitive impairments and healthy individuals. The CFQ consists of 25 items, of which 17 create the following four subscales (n items): Distractibility (7), Distractibility in Social Situations (4), Names and Words (3) and Orientation (3). Respondents indicated how often a particular ‘failure’ had happened to them in the past 6 months on a scale from very often (4) to never (0). Higher scores indicate more frequent failures. Internal consistency of the Dutch subscales is sufficient.31

Statistical analyses
SPSS (version 23; SPSS Inc., Chicago, IL) was used for statistical analyses, comparing survivors with controls. Two-sided p-values < .01 were regarded as significant. Differences between the two survivor groups and controls on QoL subscales were analyzed with Kruskal-Wallis H tests because of the ordinal nature of the variables. For significant outcomes, post-hoc pairwise comparisons were calculated as described by Dunn 32. Cohen’s effect size r was calculated as $Z/\sqrt{n}$. Cohen’s $r > .10$ is considered as small, $>.30$ as medium, $>.50$ as large, and $>.70$ as very large.33
For QoL subscales that demonstrated a significant difference between survivors and controls, potential risk factors (i.e. AaA, AaD, gender, doses of CRT, MTX IT and MTX IV) were analyzed using linear regression (Enter method). Correlations with a p-value < .05 were recalculated individually using Spearman’s partial rank correlations to reduce sensitivity to outliers. As SPSS does not readily provide a method for calculating partial non-parametric correlations, we used syntax to be able to control for AaA and gender (and where applicable for AaD, MTX IT and MTX IV). The /MATRIX OUT subcommand in the NONPAR CORR procedure was used to save a matrix of Spearman’s rho correlations as the current data set. The PARTIAL CORR procedure can read this matrix as the input data by using the /MATRIX IN subcommand.34

**Results**

Characteristics of the groups are reported in Table 1. The groups did not differ significantly from the corresponding groups that did not complete the QoL questionnaires on AaA, AaD, dose of MTX IT, dose of MTX IV, dose of CRT, or estimated IQ (data not shown). The groups with QoL data only differed significantly from each other on AaA ($F(2,125) = 11.7$, $p < .001$, see Table 1). Employment rates, around 90%, did not differ between these groups ($\chi^2(4) = 1,766$, $p = .779$).

**Quality of Life scales**

Mean ranks and H statistics of group differences on all subscales are reported in Table 2. CRT-treated survivors reported significantly more problems in Physical Functioning, Role Limitations due to Physical Health, Energy/Fatigue, and General Health. Furthermore, they reported significantly more Physical Fatigue and Mental Fatigue than controls. The CT-treated survivors reported significantly more Mental Fatigue than controls. Comparing the CT-treated group directly with the CRT-
treated group, we found that the CT-group reported significantly better Physical Functioning and less Role Limitations due to Physical Health. CRT-treated survivors had achieved a significantly lower educational level.

**Risk Factors**

For CT-treated survivors, partial correlations were calculated between Mental Fatigue and AaA, AaD, gender, MTX IT and MTX IV. None of the partial correlations were significant (.044 < rho < .335; .052 < p < .803).

For CRT-treated survivors, partial correlations were calculated between all subscales demonstrating a significant difference between CRT-treated survivors and controls, and AaA, AaD, gender, doses of CRT, MTX IT, and MTX IV. Controlling for the other risk factors, significant correlations were found between dose of MTX IT and Energy/Fatigue (rho = .441, p = .010), General Fatigue (rho = -.365, p = .037), and Physical Fatigue (rho = -.375, p = .032). Contrary to our expectations, the directions of the correlations indicated that higher doses MTX IT were associated with less fatigue. Dose of CRT was a significant risk factor for more distractibility.
Table 2. Kruskal-Wallis H tests for all questionnaire subscales. H-statistics and asymptotic significance values (2-sided) are reported for each test. Pairwise group comparisons were done using Mann-Whitney U tests (Dunn method), with asymptotic p-values, and Cohen’s effect sizes (r).

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<th>CT Mean Rank</th>
<th>CRT Mean Rank</th>
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**MFI-20‡**

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**CFQ‡**

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**Educational level‡**

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*Note. CON=controls (n=47); CRT= survivors treated with cranial radiation therapy (n=38); CT= survivors treated with chemotherapy only (n=43)
* = significant at p < .05, ‡ = a higher score represents a more favorable evaluation. † = a higher score represents a less favorable outcome.
(rho = .390, p = .025). There were significant associations between gender and Physical Functioning (rho = -.393, p = .024), Role Limitations due to Physical Health (rho = -.431, p = .012), and General Health (rho = -.366, p = .036).

Other partial correlations were not significant. The correlations between dose of CRT and the other significant QoL scales varied between -.069 (p = .701) and .325 (p = .065), the latter for General Health. For AaD, the rho’s varied from .001 (p = .996) to -.246 (p = .168), the latter for Energy/Fatigue. Similar ranges were found for AaA and MTX IV. Rho’s for other QoL correlations with MTX IT ranged from -.005 (p = .978) to .337 (p = .055), the latter for Role Limitations due to Physical Health, also associating higher doses MTX IT with more favorable outcomes.

The significant correlations implicating gender to be a risk factor were further explored by contrasting males and females on the respective subscale scores. Female survivors (mean rank = 15.55) reported significantly lower scores than male survivors (mean rank = 23.89) on Role Limitations due to Physical Health (U = 101.00, p = .009). On Physical Functioning, female survivors (mean rank = 15.48) also reported significantly lower scores than male survivors (mean rank = 23.97; U = 99.50, p = .016). Another significant difference was found on General Health, where women (mean rank = 16.12) reported lower scores than men (mean rank = 23.25; U = 112.50, p = .048). The mean ranks of male and female controls did not differ significantly for Role Limitations due to Physical Health (p = .305), Physical Functioning (p = .498), or General Health (p = .183).

**Discussion**

Self-reports on HR QoL were analyzed of a group of 43 CT-treated survivors and a group of 38 CRT-treated survivors of childhood lymphoid malignancies, 22-26 years post-treatment. Their scores were compared with 47 healthy controls. CT-treated
survivors reported significantly more mental fatigue, but did not differ from controls on any other scale. CRT-treated survivors, however, reported significantly worse scores on physical functioning, role limitations due to physical health, energy/fatigue, general health, physical fatigue, and mental fatigue, and lower educational achievement. No impact of treatment was seen on employment rates. On general health, physical functioning and role limitations due to physical health, female CRT-treated survivors reported lower scores than male CRT-treated survivors. Neither CT-treated survivors nor CRT-treated survivors reported any mood disturbances.

It is remarkable that neither of the survivor groups reported heightened levels of cognitive failures, apart from a trend on distractibility. Neuropsychological deficits have been established objectively in our group of CRT-treated survivors, but these do not seem to cause any subjective complaints. Several studies have reported a similar discrepancy (e.g. Link et al., 2006; Kenzik et al., 2015). Possibly, survivors have no record of their level of premorbid cognitive functioning to compare their current functioning with, and they could have become accustomed to their limitations.

Our results were largely in line with Blaauwbroek et al. (2007), who also reported reduced scores on physical functioning, energy/fatigue and general health, assessed with the RAND-36, in survivors of various types of cancer more than 20 years after diagnosis. They also reported worse outcomes in female survivors. The only difference was that their study reported reduced social functioning, whereas our group reported more role limitations due to physical health. Our results did not agree with Harila et al. (2010), whose survivor group reported QoL ratings similar or even higher than controls on the RAND-36, but they suspected socially desirable response bias. Their cohort, however, did report significantly more role limitation due to emotional problems.
A great advantage of the methodology of Blaauwbroek et al. and Harila et al. was that they graded late effects using the Common Terminology Criteria for Adverse Events, Version 3 (CTCAEv3). The CTCAEv3 grades adverse effects from 0 (minimal, usually asymptomatic) to 4 (potentially life threatening). Blaauwbroek et al. found that CRT-treated survivors of leukemia reported significantly more severe late effects (47%) than CT-treated survivors (17%). Although these criteria were not applied in our samples, it seems conceivable that increased rates of severe late effects were also present in our CRT-treated group, and that these physical late effects were associated with worse physical functioning, energy/fatigue, and general health.

Gender and dose of CRT could be confirmed as risk factors for lower QoL, whereas we did not find significant associations with AaA or AaD, which is in line with findings by Krull et al. (2013). Unexpectedly, we found a significant association between higher doses of MTX IT and less fatigue in the CRT-treated group. This could be just coincidence, but a similar finding has been reported by Kanellopoulos et al. (2016). Perhaps there is a third factor, e.g. a CT agent, which dose is increased when dose of MTX IT is decreased, with a detrimental effect on fatigue, mediating the association. Future research should further explore this possibility. In general, the individual toxicities of different chemotherapeutic agents, and their dose effects as well as administration methods, need to be better understood.

The survivors did not report more depression than controls. Parker et al. (2003) described that survivors who were older, married, or who had more social support reported less depressive symptoms and anxiety, and better QoL in the mental health domain, independent of demographic and medical variables. Our observation that many survivors (58%) brought someone close to them to the assessment might be a sign of their social support.
The rates of employment we found in our samples were remarkably high. Krull et al. (2013) reported that 16.8% of non-irradiated and 22.8-28.0% of irradiated survivors they studied were unemployed, versus ±10% in all three groups of our sample. However, also Krull reported that employment status of their sample was very similar to age- and gender-adjusted rates in the United States population. Therefore, seeming differences are probably attributable to differences in economy.

Comparing scores of CRT-treated and CT-treated survivors directly with each other, the CT-treated survivors rated their physical functioning and limitations due to physical health significantly better. The CT-treated group also achieved a significantly higher educational level. On the other scales, their scores fell in between the scores of CRT-treated survivors and controls, but effect sizes for the differences with either group were small. Similar outcomes were reported by Blaauwbroek et al. (2007), who only found a significantly better general health perceived by CT-treated than CRT-treated survivors. However, overall, the degree of complaints relating to HR QoL seems to be considerably smaller in the CT-treated group, and the domains that demonstrated significant differences with CRT-treated survivors are not trivial. Physical functioning, role limitations due to physical health, and educational attainment intuitively seem to be of high impact on the overall experience of QoL. Therefore, we conclude that these outcomes are an important indication of higher QoL for cohorts not treated with CRT.

Methodological considerations

The QoL data were analyzed with non-parametric methods. As these are less sensitive and more conservative than parametric tests, this probably means that the significant results we found are quite robust. However, future research might want to incorporate the late effects grading system CTCAEv3 and other information on comorbidities, as these are likely to influence perceived HR QoL. A
strength of our study was the use of an adequate control group, including siblings, spouses, and friends of the survivors, as emphasized by Moleski et al. (2000). Quinn et al. (2013) noted that the majority of standardized HR QoL instruments are nonspecific to the developmental stage and unique late effects of young adult cancer survivors, such as self-image or fertility, and might not be comprehensive. Therefore, existing HR QoL instruments should be refined for future late effects research in order to adequately incorporate aspects of HR QoL that are unique to childhood cancer survivors transitioning from childhood into adolescence, from adolescence into adulthood, and from adulthood into old age.

Another issue with the use of self-report measures of QoL in the population of childhood cancer survivors is self-deception response bias. O’Leary et al. (2007) used the Self-Deception Enhancement scale to assess this issue and found that childhood cancer survivors’ scores were significantly higher than normative groups and that these elevated scores correlated significantly with reports of health-related QoL. Therefore, very positive outcomes should be interpreted in light of a systematic tendency to deny difficulties. However, this should concern all childhood cancer survivors, and therefore the comparison of two differently treated groups should not be affected by this problem.

Conclusion
Twenty-six years after CRT, survivors reported significantly worse QoL than controls in the domains of general health, physical functioning, fatigue, and role limitations due to physical health, whereas long-term survivors treated with CT (22 years post-diagnosis) only reported heightened levels of mental fatigue. On other scales, CT-treated survivors did not report reduced QoL compared with controls. Higher doses of CRT and female gender were confirmed as risk factors. Overall, the results indicate that the abolishment of CRT (around 1983) has ensured a higher standard
of QoL for very long-term survivors of childhood lymphoid malignancies in the Netherlands and Belgium.
References

24. Wald FDM, Mellenbergh GJ: De verkorte versie van de Nederlandse vertaling van de Profile of Mood States (POMS). Nederlands Tijdschrift voor de Psychologie 45:86-90, 1990