SURVIVOR AND SURVIVAL IN PEDIATRIC ONCOLOGY

Ph.D. Thesis Booklet

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1. Introduction

1.1. Overview of the topic

1.1.1. What is the topic?

Advances in pediatric oncology have led to a substantial improvement in survival rates, resulting in a rapidly growing population of childhood cancer survivors (CCSs). While survival has become the expected outcome for many pediatric malignancies, increasing attention has shifted towards the long-term consequences of cancer and its treatment. These consequences extend beyond medical late effects and encompass educational achievement, employment, family formation, mental health, and overall quality of life of survivors.

In parallel, the treatment landscape of high-risk neuroblastoma (HR-NBL) has evolved with the introduction of immunotherapeutic approaches, including dinutuximab beta. While clinical trials have demonstrated its efficacy, real-world data on effectiveness, safety and treatment patterns remain limited particularly in Central and Eastern Europe.

1.1.2. What is the problem to solve?

Despite improved survival, many CCSs experience persistent difficulties in social, psychological, and socioeconomic reintegration during adulthood. These challenges are often underrecognized and inconsistently addressed in routine follow-up care. Existing studies frequently focus on isolated outcomes, specific cancer types, or selected populations, resulting in fragmented evidence and limited generalizability.

Similarly, although dinutuximab beta has become an integral component of HR-NBL therapy, evidence from real-world clinical practice is scarce. Variability in treatment implementation, subsequent therapies, and toxicity management complicates the interpretation of outcomes and limits the translation of trial results into everyday clinical decision-making.

1.1.3. What is the importance of the topic?

Understanding the long-term consequences of childhood cancer is essential for delivering comprehensive survivorship care that extends beyond disease control.

Educational attainment, employment stability, family formation, and psychological well-being are central determinants of adult functioning and social participation. Identifying vulnerable subgroups is crucial for targeted interventions.

In high-risk neuroblastoma, while dinutuximab beta has demonstrated efficacy in controlled clinical trials, outcomes, toxicity profiles, and treatment pathways in real-world clinical practice may differ substantially due to broader patient heterogeneity, variable supportive care, and diverse subsequent therapies, underscoring the need for real-world evidence to inform everyday clinical decision-making.

1.1.4. What would be the impact of our research results?

By synthesizing evidence across multiple life domains, this thesis provides a comprehensive overview of long-term psychosocial and socioeconomic outcomes among CCSs, highlighting areas of persistent disadvantages and unmet needs. These findings can support the development

of structured, lifelong survivorship programs with a focus on social reintegration.

In addition, the real-world analysis of dinutuximab beta treatment contributes clinically relevant evidence on outcomes and safety in HR-NBL, complementing trial data and supporting evidence-based clinical practice. Together, the two studies aim to bridge gaps between survival, quality of survivorship, and modern therapeutic strategies in pediatric oncology.

2. Objectives

2.1. Study I. – Burden of Childhood Cancer and the Social and Economic Challenges in Adulthood

The objective of Study I was to systematically collect, critically appraise, and quantitatively synthesize the available evidence on long-term psychosocial and socioeconomic outcomes among childhood cancer survivors in adulthood. The study aimed to compare educational attainment, employment status, income level, family formation, health-risk behaviors, and quality of life between survivors and appropriate control populations, including population-based controls and siblings. Special

attention was given to differences across major cancer subgroups. Through meta-analytic techniques, the study sought to quantify the magnitude of long-term disadvantages, explore between-study heterogeneity, and assess the robustness of findings across outcome domains and comparator groups.

2.2. Study II. – Dinutuximab beta for the Treatment of High-Risk Neuroblastoma

The objective of Study II was to evaluate the real-world effectiveness and safety of dinutuximab beta in the treatment of children with high-risk neuroblastoma in Hungary. Using retrospective data from the Hungarian Childhood Cancer Registry, and collected from the participating centers of the Hungarian Pediatric Oncology Network (HuPON) the study aimed to describe treatment responses, overall survival (OS), and event-free survival (EFS) in patients receiving dinutuximab beta either as part of first-line maintenance therapy or in the relapsed or refractory setting. In addition, the study sought to characterize the safety profile of dinutuximab beta in routine clinical practice and to explore the influence of

treatment setting and key disease-related factors on survival outcomes.

3. Methods

3.1. Study I

For Study I, a systematic review and meta-analysis were conducted in accordance with international methodological standards (Cochrane Handbook and PRISMA 2020 Guidelines). Prestudy protocol was registered on PROSPERO (CRD4202128379). A comprehensive literature search was performed in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The initial search was carried out on 23 October 2021 and subsequently updated to include publications up to 31 July 2023. The search strategy was designed to maximize sensitivity and included terms related to childhood cancer, survivorship, and long-term psychosocial, socioeconomic, and quality-of-life outcomes. No restrictions were applied regarding language, publication date, or study design. Eligible studies included childhood cancer survivors diagnosed before adulthood and reported

outcomes related to education, employment, income, family formation, health-risk behaviors, mental health, or quality of life, with comparisons to population-based controls, matched controls, or siblings. Studies focusing exclusively on adult-onset cancer or patients undergoing active oncological treatment were excluded. Study selection was performed independently by multiple reviewers in a two-step process consisting of title–abstract screening followed by full-text assessment, with disagreements resolved by consensus. Data extraction was conducted using a standardized data collection form and included study characteristics, participant demographics, cancer type, comparator group, and outcome data. Risk of bias was assessed using the Quality in Prognostic Studies (QUIPS) tool in accordance with Cochrane Handbook recommendations. Meta-analyses were performed for outcomes reported by at least three independent studies using random-effects models. Pooled odds ratios were calculated for dichotomous outcomes, while mean differences or standardized mean differences were used for continuous outcomes. Analyses were stratified by cancer type and comparator group, statistical

heterogeneity was assessed using the I^2 statistic, and results were presented using forest plots.

3.2. Study II

For Study II, a multicenter, retrospective observational cohort study was conducted using real-world data from the Hungarian Childhood Cancer Registry and participating Hungarian Pediatric Oncology Network centers. Pediatric patients diagnosed with high-risk neuroblastoma who received dinutuximab beta either as first-line maintenance therapy or in the relapsed or refractory setting between October 2018 and February 2023 were eligible for inclusion. All patients were required to have measurable or evaluable disease at the initiation of dinutuximab beta therapy. Clinical, pathological, treatment-related, and outcome data were retrospectively collected using a standardized data collection sheet. Tumor response was assessed locally according to the International Neuroblastoma Response Criteria (INRC). Overall survival and event-free survival were defined from the time of diagnosis and analyzed using the Kaplan–Meier method, with patients censored at

last follow-up if no event occurred. Survival outcomes were stratified by treatment setting and MYCN amplification status, and Cox proportional hazards regression models were applied to explore associations between clinical variables and survival. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTC-AE v5.0). All statistical analyses were performed using the R statistical software environment.

4. Results

4.1. Study I.

For Study I, 280 studies published between 1986 and 2023 were included, comprising a total of 389,502 childhood cancer survivors compared with population-based controls, matched controls, or siblings. Across all examined domains, childhood cancer survivorship was associated with persistent disadvantages in adulthood, most consistently among survivors of central nervous system (CNS) malignancies.

In the educational domain, childhood cancer survivors demonstrated similar odds of achieving at least high

school graduation compared with population-based controls (OR = 1.00; 95% CI 0.74–1.37), but lower odds compared with siblings (OR = 0.33; 95% CI 0.10–1.12). At the tertiary level, survivors had reduced odds of completing lower-level tertiary education compared with population-based controls (OR = 0.85; 95% CI 0.68–1.06) and siblings (OR = 0.54; 95% CI 0.42–0.69), and similarly reduced odds for higher-level tertiary education. Survivors were also significantly more likely to require special education services (OR = 3.28; 95% CI 2.65–4.06). CNS tumor survivors showed the most pronounced educational disadvantages, with significantly lower odds of completing high school (OR = 0.48; 95% CI 0.39–0.58) and lower-level tertiary education (OR = 0.53; 95% CI 0.44–0.63).

In terms of employment, overall employment rates were similar to population-based controls (OR = 1.03; 95% CI 0.80–1.34), but significantly lower when compared with siblings (OR = 0.58; 95% CI 0.40–0.83). Survivors of CNS tumors had markedly lower odds of employment (OR = 0.44; 95% CI 0.26–0.76) and substantially higher

odds of health-related unemployment (OR = 8.96; 95% CI 5.62–14.01). Across comparisons, survivors were also less likely to belong to middle- or high-income categories, particularly when compared with siblings (OR = 0.61; 95% CI 0.48–0.79).

Family formation outcomes revealed significant long-term effects. Survivors were less likely to be married than population-based controls (OR = 0.72; 95% CI 0.63–0.84) and siblings (OR = 0.63; 95% CI 0.55–0.72), with the lowest odds observed among CNS tumor survivors (OR = 0.32; 95% CI 0.21–0.47). Survivors were also less likely to have children (OR = 0.60; 95% CI 0.49–0.74 vs population controls; OR = 0.43; 95% CI 0.40–0.46 vs siblings) and had a lower mean number of children (MD = −0.44; 95% CI −1.27 to −0.40). Divorce rates did not differ significantly between survivors and controls.

Regarding health-risk behaviors, survivors were less likely to be current smokers compared with population-based controls (OR = 0.72; 95% CI 0.54–0.96) and showed lower, though mostly non-significant, odds of alcohol and marijuana consumption. Despite this,

survivors demonstrated a higher prevalence of antidepressant use compared with population-based controls (OR = 1.19; 95% CI 1.09–1.29), particularly among CNS tumor survivors (OR = 1.27; 95% CI 1.19–1.35).

Quality-of-life analyses showed that overall self-reported QoL was comparable to controls, while survivors of CNS malignancies consistently reported lower QoL scores, with parent-proxy assessments indicating the greatest impairment.

4.2. Study II

For Study II, 37 pediatric patients with high-risk neuroblastoma treated with dinutuximab beta were analyzed. At data cutoff, the objective response rate (ORR) was 51.4%, with all responses being complete responses and a disease control rate of 54.1%. The median overall survival for the entire cohort was 11.8 years (95% CI: 4.6-n.a.), and the median event-free survival was 9.8 years (95% CI: 2.9-n.a.), with 5-year overall survival and event-free survival rates of 63.3% (95% CI: 49.1-81.7%) and 56.2% (95% CI: 42.1-75.0%), respectively. Survival

outcomes did not differ significantly between patients treated in the first-line and relapsed or refractory settings, nor between MYCN-amplified and non-amplified subgroups. Dinutuximab beta demonstrated a manageable safety profile consistent with prior reports, with grade 3–4 adverse events primarily including blood and lymphatic system disorders (37.8%), hypoxia (37.8%), hepatobiliary disorders (29.2%), hypotension (27.0%), capillary leak syndrome (13.5%), diarrhea (8.1%), generalized edema (5.4%), and urinary tract infection (5.4%); grade 4 events were infrequent and occurred in a minority of patients (13.5%).

5. Conclusions

5.1. Study I.

This systematic review and meta-analysis demonstrates that childhood cancer survivorship is associated with substantial and persistent psychosocial and socioeconomic challenges extending into adulthood. Across education, employment, family formation, health-related behaviors, and quality of life, childhood cancer survivors consistently showed less favorable outcomes

compared with their peers, particularly when compared with siblings. Survivors of central nervous system malignancies were the most vulnerable subgroup, exhibiting the greatest disadvantages across multiple domains, likely reflecting the long-term neurocognitive and functional consequences of disease and treatment. While survivors reported comparable overall self-perceived quality of life, objective indicators of social reintegration, including educational attainment, employment stability, income level, and family formation revealed significant gaps. These findings underscore that survival alone is an insufficient endpoint in pediatric oncology and highlight the need for structured, complex and comprehensive lifelong survivorship care focusing on social, psychological, and economic reintegration.

5.2. Study II.

This multicenter real-world analysis confirms that dinutuximab beta is an effective and feasible treatment option for children with high-risk neuroblastoma in routine clinical practice. Treatment was associated with meaningful disease control and encouraging long-term

survival outcomes in both first-line maintenance and relapsed or refractory settings, despite the heterogeneity and complexity of real-world patient populations. The safety profile observed was consistent with previously reported clinical trial data, with adverse events largely manageable through supportive care. Survival outcomes were not significantly influenced by treatment line or MYCN amplification status, although interpretation is limited by sample size. Collectively, these results support the real-world applicability of dinutuximab beta and emphasize the importance of continued evaluation of immunotherapy strategies beyond controlled clinical trial settings.

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