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01

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Adolescent and Young Adult Central Nervous System Tumour Survivors: Documentation of late-effects risks and screening recommendations in British Columbia, Canada

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Survivors of adolescent and young adult (AYA) central nervous system (CNS) neoplasms are at risk for late effects (LE) - treatment-related health problems occurring more than 5 years after therapy). Since, in Canada, AYA survivors are usually followed in the community, information must be conveyed to primary care providers to guide risk-based follow-up care. Objective: To assess documentation of LE risks and screening recommendations (SR) in medical records of AYA CNS tumor survivors treated with radiation therapy. Methods: The medical records of all patients diagnosed with a CNS neoplasm (benign or malignant) at ages 15-39 years, treated between 1985 and 2010 in the province of British Columbia, surviving >5 years and discharged to the community were assessed. Documentation of LE and SR were extracted, and analyzed descriptively. Results: Among 132 survivors (52% female), treated with radiation therapy (95% partial brain, 10% craniospinal, 8% partial spine, and 4% whole brain) and chemotherapy (17%), 19% of charts included no documentation of LE risks, 26% included only non-specific documentation, and 55% had minimal documentation (1 or 2 LE). Documentation of at least one specific LE increased from 24% in 1980-1989, to 54% in 1990-1999, to 86% in 2000 – 2010. Based on treatment information, all survivors were at high-risk for LE, such as radiation induced neoplasm, meningioma and cerebrovascular events. Yet, SR were documented in only 25% of charts. Conclusions: The documentation of LE risks and screening recommendations has been limited, highlighting the need to improve written communication with primary care providers.

05

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Long-term health-related quality of life in adult survivors of pediatric intracranial germ cell tumour

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PURPOSE: To investigate health-related quality of life (HRQOL) in survivors of intracranial germ cell tumors (IGCT). METHODS: Survivors of IGCT were invited to complete the 36-Item Short Form Survey Instrument (SF-36). The SF-36 is scored from 0-100, with a higher number representing a more favorable HRQOL. RESULTS: The study cohort consisted of 12 survivors of IGCT, 6 males and 6 females. Median age was 13 years at diagnosis, and 26 years at time of study. Median follow-up was 11 years. Five patients had germinomas, and 7 had non-germinomatous germ cell tumors. All 12 patients received radiation therapy (RT), 10 to the craniospinal axis, 1 to the whole ventricles and 1 to the tumor bed alone. Nine patients received chemotherapy. Mean SF-36 scores were 67.9 (standard deviation [SD] 33.2) for physical functioning, 58.3 (SD 37.4) for role limitations due to physical health, 77.8 (SD 32.8) for role limitations due to emotional problems, 43.1 (SD 18.4) for vitality, 74.3 (SD 15.3) for mental health; 62.5 (SD 32.0) for social functioning, 74.2 (SD 33.4) for pain, and 57.1 (SD 24.0) for general health; mean scores were >1 SD lower than that of Canadian normative data for vitality, social functioning and general health. Physical component score was 43.6 (SD 13.9) and mental component score was 47.6 (SD 11.2), normalized to a US population with mean of 50 and SD of 10. CONCLUSIONS: Long-term HRQOL for survivors of IGCT is lower than that of the overall population, particularly in vitality, social functioning and general health.

06

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Prognostic factors for survival and recurrence in adult medulloblastoma

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BACKGROUND: Adult medulloblastomas account for less than 1% of adult neoplasms. They are challenging to treat due to their rarity and the heterogeneity of treatment options, all of which have limited evidence. In this retrospective review, we examined cases of adult medulloblastoma diagnosed in Alberta during a 70-year period. METHODS: We reviewed the charts of patients diagnosed with medulloblastoma between 1944 and 2014. We performed Cox and logistic regression analysis to elucidate features that may influence recurrence risk and survival. RESULTS: We found 86 and analyzed 78 cases. The median age at diagnosis was 27 (range 16 to 71). Most were male (68%). Most had surgery (92%). By COG risk stratification, 54% were standard risk while 21% were poor risk. RT was administered to 85% of patients, and craniospinal irradiation (CSI) to 81%. Chemotherapy was administered to 48%. Median survival was 4.4 years from diagnosis (range 0 to 20). At last follow-up, 39% were alive and recurrence-free. Patients who had CSI and posterior fossa boost had longer survival ($p = 0.047$ and < 0.01, respectively) and were less likely to recur ($p = 0.041$ and < 0.01). Chemotherapy was also associated with decreased recurrence ($p = 0.025$). CONCLUSIONS: Medulloblastomas carry a significant recurrence risk, especially for patients who had subtotal resection. CSI and posterior fossa boost were associated with fewer recurrences and improved survival. COG risk stratification, Chang staging, desmoplastic histology, vermian location, 4th ventricle involvement, tumor enhancement, presence of hydrocephalus and cerebrospinal fluid (CSF) involvement are not significantly prognostic.

08

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Inhibition of autophagy by mevalonate pathway inhibitors, a new therapeutic approach to sensitize glioblastoma cells to temozolomide induced apoptosis

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Glioblastoma multiforme (GBM) is the deadliest brain tumor with an approximate 14 month survival rate after diagnosis and treatment. Temozolomide (TMZ), the chemotherapeutic drug of choice for GBM, is an alkylating agent that causes DNA damage. TMZ treatment results in the induction of apoptosis in GBM cells, however, it induces autophagy and consequently chemoresistance. Statins are mevalonate (MEV) cascade inhibitors with beneficial effects on the enhancement of the survival rate of patients with different types of cancer. Here, we determined the effect of simvastatin (Simva), a blood brain barrier permeable statin, on the sensitization of GBM cells to TMZ induced apoptosis through inhibition of autophagy flux. We pretreated two GMB cell lines, U251 and U87 cells, with low doses of Simva (1 and 2.5 M, respectively) with or without different intermediates of the mevalonate cascade and then treated cells with TMZ (100 M) for 48-96 hrs. A signficiantly reduced viability and increased in the population of apoptotic dead cells were observed in GBM cells treated with the Simva-TMZ compared to cells treated with TMZ alone. Addition of MEV, Farnesyl pyrophosphate, Geranylgeranyl pyrophosphate and cholesterol did not attenuate these effects significantly. Sima-TMZ treatment did not alter the total cholesterol pool in U87 and U251 cells compared to controls. Western blot analysis, immunocytochemistry and transmission electron microscopy revealed that Simva-TMZ inhibited autophagic flux. Overall, the results suggest that sensitization of GBM cells to TMZ-induced apoptosis by Simva is independent on the cholesterol biosynthetic pathway but may involve inhibition of autophagy.

10

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Toca 5: Toca 511 combined with Toca FC versus standard of care in patients undergoing planned resection for recurrent glioblastoma or anaplastic astrocytoma

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Toca 511 (vocimagene amiretrorepvec) is an investigational, conditionally lytic, retroviral replicating vector (RRV). RRVs selectively infect cancer cells due to innate and adaptive immune response defects in cancers that allow virus replication, and the requirement for cell division for virus integration into the genome. Toca 511 spreads through tumors, stably delivering an optimized yeast cytosine deaminase gene that converts the prodrug Toca FC (investigational, extended-release 5-FC) into 5-FU within the tumor microenvironment. 5-FU kills infected dividing cancer cells and surrounding tumor, myeloid derived suppressor cells, and tumor associated macrophages, resulting in long-term tumor immunity in preclinical models. Data from a Phase 1 resection trial showed six durable CRs and extended mOS compared to historical controls. The FDA granted Breakthrough Therapy Designation for Toca 511 & Toca FC in the treatment of patients with rHGG. Toca 5 is an international, randomized, open-label Phase 3 trial (NCT02414165) of Toca 511 & Toca FC versus SOC in patients undergoing resection for first or second recurrence of rHGG. Patients will be stratified by IDH1 status, KPS, and geographic region. Primary endpoint is OS, and secondary endpoints are durable response rate, durable clinical benefit rate, duration of durable response, and 12-month survival rate. Key inclusion criteria are histologically proven GBM or AA, tumor size ≥1cm and ≤5cm, and KPS ≥70. Immune monitoring and molecular profiling will be performed. Approximately 380 patients will be randomized. An IDMC is commissioned to review the safety and efficacy data which includes 2 interim analyses. Enrollment is ongoing.

11

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Study of Polynucleotide Kinase/Phosphatase (PNKP) Mutations Found in a Patient with Microcephaly, Seizures, and Developmental Delay (MCSZ) and Glioblastoma

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The enzyme polynucleotide kinase/phosphatase (PNKP) plays a key role in DNA repair by resolving the chemistry at DNA strand breaks. Mutations in PNKP (chromosome 19q13.4) are known to cause MCSZ, a serious neurodevelopmental disorder, but to date there has been no link to cancer initiation or progression. However, a child with MCSZ recently presented at Seattle Children's Hospital with a 3-cm glioblastoma. The child was shown to have two germline mutations in PNKP. To study the effects of the PNKP mutations found in this patient, we generated mutant PNKP cDNAs carrying either the individual mutations or the double mutation using site directed mutagenesis. These cDNAs were incorporated into bacterial and mammalian expression vectors. The bacterially expressed mutant proteins as well as the wild type have been purified and are undergoing testing for PNKP DNA kinase and phosphatase activity. The PNKP cDNAs, fused to GFP, were expressed in Hela and HCT116 human cancer cell lines. High-content analysis and micro-irradiation techniques are being used to determine PNKP localization within the cells and recruitment to damaged DNA. Our preliminary results indicate that the mutations alter the ratio of nuclear to cytoplasmic PNKP compared to the wild-type protein.

12

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The potential role of exercise in the supportive care of neurological cancer survivors: delivering effective and appropriate programming through the Alberta cancer exercise (ACE) study

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BACKGROUND: Exercise has been shown to benefit health-related fitness, psychosocial health, and disease outcomes in cancer survivors. PURPOSE: To review the evidence on exercise for individuals diagnosed with Neurological Cancer (NC); present data on NC participants in the ACE pilot and ongoing implementation study; and propose a framework to incorporate exercise into the