care of NC survivors in Alberta. METHODS: The ACE program is open to survivors with any cancer diagnosis at any stage of treatment. Exercise programming consists of two training sessions per week, with the pilot and implementation studies being 8 and 12 weeks in duration respectively. Outcomes are assessed at study baseline, post-exercise intervention, and 24-week follow-up, and include recruitment and follow-up rates, health-related fitness, psychosocial outcomes, and cancer symptoms. RESULTS: NC survivors represented 7 of 80 participants in the ACE pilot; however, only 3 of the 7 (43%) completed the study. Findings suggested a need for consideration of supervised exercise for some survivors with NC. To date, 14 NC survivors have enrolled in the ACE implementation study. Participants are screened and then referred to either supervised clinic-based or community-based exercise. Seven of 9 participants have completed the ACE intervention, and 5 of 5 have completed the 24-week follow-up. NC participants improved or maintained health-related physical fitness, and reported reduced symptom burden and fatigue. CONCLUSION: Preliminary results suggest exercise training is feasible and beneficial for NC survivors. To optimize recruitment and outcomes, efforts are needed to better identify, screen, and refer survivors to appropriate exercise programming.

16

doi:10.1017/cjn.2018.259

Combining an oncolytic vaccinia virus with image-guided radiotherapy: a multi-modal therapeutic approach for treating glioma

Q. Storozynsky, D. Evans, N. Snyder, K. Potts, K. Agopsowicz, R. Godbout, M. Hitt.* storozyn@ualberta.ca

* CRINA Travel Award Recipient

Malignant gliomas (MG) are highly invasive and aggressive brain tumors. Despite the current standard of care, the prognosis for patients with MG is abysmal– highlighting the need for novel, more effective treatment options to combat this aggressive disease. Oncolytic virus (OV) therapy is an advancing treatment option that harnesses tumor-selective viruses to kill cancer cells while simultaneously facilitating a systemic anti-tumor immune response. Many studies have noted synergistic effects when OV"s are combined with radiotherapy in preclinical cancer models, warranting further investigation of this multi-modal approach. Image-guided radiotherapy (IGRT) uses computer-modulated imaging techniques to precisely deliver ionizing radiation to treat cancer. Despite the precision IGRT offers, cancer cells can still be „missed" due to tumor microextensions or radioresistant cell populations– such as glioma stem cells or therapy-induced senescent cancer cells –and may contribute to recurrence or progression. Here we propose to combine our mCherry-tagged mutant vaccinia virus (deltaF4L-deltaJ2R-mCherry), which exhibits tumor-selectivity due to mutations in key viral nucleotide biosynthesis genes, with IGRT executed using state-of-the-art Small Animal Radiation Research Platform (SARRP) technology. We hypothesize that combining deltaF4L-deltaJ2R-mCherry with IGRT will produce better tumor control than either modality alone, by generating additive or synergistic effects in which IGRT destroys the majority of the tumor mass while our OV seeks out and targets any remaining cancer cells that have been missed or are resistant to radiotherapy.

17

doi:10.1017/cjn.2018.260

Tailored exercise for survivors with brain tumours: A case series

Spychka, R.A., Sellar, C.M., Easaw, J.C., Murtha, A.D., Culos-Reed, S.N., McNeely, M.L. spychka@ualberta.ca

Purpose: Exercise has been shown to be beneficial for the physical and psychological health of cancer survivors, however, little research has been conducted on the effects of exercise in the brain tumour population. Survivors with brain tumours present with unique challenges in terms of mobility and function that may compromise their ability to safety take part in community-based exercise. Methods: Three survivors with primary brain tumours will be profiled in this case series presentation. Participants were screened using a cancer specific intake questionnaire and the Physical Activity Readiness Questionnaire, and triaged to supervised clinic-based or community-based exercise. All participants completed the 12-week intervention for the Alberta Cancer Exercise (ACE) study. Measurements were taken at baseline, and post-intervention including measures of body composition, aerobic fitness, musculoskeletal fitness, balance and flexibility. Self-reported measures included questionnaires to assess impact on physical functioning, symptoms and quality of life, and to evaluate satisfaction with programming. Results: One participant was referred to supervised clinic-based exercise programming due to a high risk of falls, and two participants were deemed safe and approved for community-based supported exercise programming at a preferred location closer to their home. Preliminary results suggest high program satisfaction, maintenance and/or benefit of physical fitness, balance, and symptom control. Conclusions: Further efforts are needed to better tailor programming to the needs of the survivor and consideration given to the advantages of the supervised clinic-based environment when compared to the survivor preference for a "closer to home" community-based setting.

19

doi:10.1017/cjn.2018.261

Autophagy related metals in IDH1 mutant glioma: Chloroquine and TMZ as a potential novel strategy to treat IDH1 mt gliomas

Bautista W, Abu-Asab M, Amable L, Ross L, Riggins G, Kozlov S. wendy.bautista@nih.gov

Glioblastoma is considered among the most aggressive cancers, dismal prognosis and overall survival is only 14 months, 80% of primary low grade gliomas and seccondary GBMs that progress from low grade to grade II or III WHO classification have isocitrate dehydrogenase, (IDH1) or IDH2, mutations [1]. IDH1 mutant glioma is characterized by impaired glycolysis activity resulting in an abnormal production of 2-hydroxyglutarate (2-HG) [2] resulting in an undifferentiated phenotype with permanent hyper-methylation status and enhanced proliferation and invasion[3]. Interestingly, the IDH1 mutant phenotype of U87MG glioma cells shows resistance to autophagy induced cell death even in starving and low oxygen conditions [4]. Recent evidence has demonstrated increased autophagy activity on IDH1 mt cytotoxic

activity when cells are exposed to autophagy inhibitors such as chloroquine [5]. To this date it remains elusive whether increased autophagy phenotype is the result of IDH1 mutation or if it either represents a secondary co-existing condition in the setting of the IDH1 mutation. Autophagy is also a mechanism of detoxification induced by chronic heavy metal exposure in both normal and cancer cells. Thus, we hypothesized that autophagy activity in IDH1 mt glioma is partially induced by chronic heavy metal exposure, leading to increased cell survival and abnormal DNA repair. Our approach included characterization and quantification of metal content on IDH1 mt glioma cell lines and tissues, in addition to correlation analyses of the celullar metallome with autophagy markers, ROS and DNA repair of IDH1 mt glioma cells allowed us to explore targets responsible for cell survival and DNA repair response. Furthermore, we evaluated the potential therapeutic value of Chloroquine (CQ) and bafylomicin for IDH1 mutant gliomas targeting autophagy pathway in combination with TMZ and radiation. We demonstrated that 2-HG induces autophagy activity via LC3B activation, and autophagy inhibiton by beclin gene silencing results in a reduction of 2-HG leading to cell starvation and apoptosis. Remarkably, we observed a positive correlation on at least six different metals with autophagy induced LC3B and beclin1 expression that significantly differed between the mutant and the wt genotype in glioma cell lines. ROS and DNA repair were also positively associated with at least 6 different metals and only seen in the IDH1 mt cell lines, then suggesting a possible explanation for the increase on autophagy, analysis of both LC3B and beclin 1 expression demonstrated a positive correlation with Mo98, Fe54, and Zn 66 on IDH1 mt cell lines and a positively correlation with Mo98 and V concentrations in relation to H2AX expression. Co, SeO Mo, V and Mg were positively correlated to ROS expression. TMZ and CQ induced autophagy pathway activation as measured by LC3B, Beclin, Atg expression. Silencing beclin in IDH1 mutant glioma cell lines induced apoptosis and reduction on 2-HG production after treatment with TMZ and radiation. Overall the results contained in this study 1) identify cellular metal content in relationship to mechanisms leading to increased autophagy on IDH1 mt glioma cells. 2) evaluate the combination of CQ and TMZ to potentially target and inhibit autophagy as a mechanism downstream the 2-HG production in IDH1 mt glioma cells.

20

doi:10.1017/cjn.2018.262

Disparities in survival for patients with glioblastoma multiforme

Mostafa Fatehi, Camille Hunt, Roy Ma, Brian Toyota.
fatehi@alumni.ubc.ca

Background: Glioblastoma multiforme (GBM) is the most common malignant primary brain cancer in adults. Recent efforts have elucidated genetic features of tumor cells and thus enhanced our knowledge of GBM pathophysiology. The most recent clinical trials report median overall survival between 14 and 20 months. However, real-world outcomes are quite variable and there is a paucity of data within the literature. Methods: Three hundred seventy two GBM patients were diagnosed in the province of British Columbia between January 2013 and January 2015. We have performed a retrospective review on the survival outcomes of the 278 patients who underwent surgical resection as part of the initial treatment. Results: Our results indicate a median age of 61.8y at time of diagnosis with a slight preponderance of males. The median overall survival was 10 months for patients who underwent surgery. As expected, patients over the age of 65 and those with worse initial Karnofsy Performance Status (KPS) scores had a poorer prognosis. Moreover, we have found extent of resection (EOR), treatment strategies and treatment location affect overall survival. Conclusion: The present study highlights factors which affect patient survival after surgery in British Columbia. Our outcomes are slightly worse than survival reported in the US. Variability in pathologic classification and in treatment strategy likely contribute to this difference. Further efforts should ensure access to the gold-standard of care.

21

doi:10.1017/cjn.2018.309

Inhibiting PARP-1 to restore temozolomide sensitivity and prevent resistance in glioblastoma

E. A. Bering, A. L. Yuan, J. G. Cairncross, M. D. Blough.
elizabeth.bering1@ucalgary.ca

Adult Glioblastomas (GBMs) remain one of the least curable brain cancers despite the discovery and use of DNA alkylating agent Temozolomide (TMZ). TMZ provides a moderate survival benefit to sensitive patients whose O6-methylguanine-methyltransferase (MGMT) gene is silenced by promoter methylation. Unfortunately, TMZ potential is stunted because of the rapid onset of tumour recurrence and acquired resistance believed to result from the upregulation of DNA damage repair by the base excision repair (BER), mismatch repair (MMR), or homologous recombination (HR) systems. Our laboratory previously demonstrated that cell lines obtained from recurrent, TMZ-resistant GBMs could be re-sensitized to TMZ when treated with an inhibitor of poly (ADP-ribose) polymerase-1 (PARP-1) – a protein instrumental in the recruitment of BER machinery. From this preliminary research, we postulate that PARP-1 inhibition may not only be used to overcome established resistance in GBM but may also be used to prevent its emergence altogether. To test this hypothesis, we utilized the MGMT-methylated GBM cell line U251N and developed an in vitro model of inducible TMZ resistance. We verified that prolonged treatment of U251N cells with TMZ resulted in the emergence of resistant colonies that resembled recurrent GBM clinically observed in TMZ-treated patients. However, when the parental U251N line was co-treated with TMZ and PARP-1 inhibitor ABT-888, resistant colonies failed to appear. Therefore, PARP-1 inhibition may possess the potential to maintain tumour sensitivity to TMZ as well as evade the otherwise inevitable development of resistance in GBM.

23

doi:10.1017/cjn.2018.270

Long-term survivors of brain metastases

Archya Dasgupta, Fabio Y Moraes, Jayson Co, Jeff Winter, Catherine Coolens, Barbara-Ann Millar, Normand Laperriere, Derek S. Tsang, Mark Bernstein, Paul Kongkham, Gelareh Zadeh, Tatiana Conrad, Alejandro Berlin, David B Shultz.
archya.dasgupta@rmp.uhn.ca

Purpose: We identified key clinicopathologic features of brain metastasis (BM) patients who are long-term survivors (LTS).