9401 ORAL

Chemotherapy Treatment Patterns in Patients With Metastatic Soft Tissue Sarcoma − the Sarcoma Treatment and Burden of Illness in North America and Europe (SABINE) Study

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Background: Chemotherapy is commonly used to treat metastatic soft tissue sarcoma. Favorable response (complete response, CR; partial response, PR; or stable disease, SD) to chemotherapy occurs in approximately 55% of patients. Understanding the management of metastatic soft tissue sarcoma is important for service planning and to support the evaluation of new interventions within their labeled indication(s). Our objective was to describe chemotherapy treatment patterns following first attainment of favorable response to chemotherapy in patients with metastatic soft tissue sarcoma.
Methods: Data were collected from medical records at 20 sites in Canada, France, Germany, Italy, the Netherlands, Spain, Sweden, UK, and the US. Inclusion criteria were: 1) Confirmed metastatic soft tissue sarcoma diagnosis with one of the following sub-types: Leiomyosarcoma, Liposarcoma, Synovial sarcoma (SS), or Undifferentiated pleomorphic sarcoma/Malignant fibrous histiocytoma (PS/MFH); 2) Favorable response after > = 4 cycles within any line of chemotherapy; 3) Age > = 13 years; 4) First line chemotherapy initiated between January 2004 and December 2009. Data were collected from initiation of first line chemotherapy to end of follow-up or death to provide a comprehensive description of treatment patterns.
Results: A total of 236 patients were included. The mean age at diagnosis of metastatic disease was 54.4 years (SD = 13.4) and 42% were male. The majority of patients (86%) were treated at European sites. The most common diagnoses were: leiomyosarcoma (46.2%), liposarcoma (23.9%), SS (13.7%), and PS/MFH (16.2%). The mean time from chemotherapy initiation to end of follow-up or death was 26.8 (SD=15.8) months. 63.6% of patients died during follow-up. Overall, patients received an average of 2.7 lines of chemotherapy. The most commonly used first line chemotherapy regimens were doxorubicin (39%), doxorubicin plus ifosfamide (21%), and gemcitabine plus docetaxel (13%). Favorable response to chemotherapy was first observed in first (82.2%) or second/third line (17.8%) chemotherapy, and classified as CR (4%), PR (29%), or SD (67%). Reasons for discontinuation of chemotherapy within the line of chemotherapy where favorable response was first observed were: disease progression (12%), predefined number of cycles given (60%), intolerable toxicity (8%), maximum clinical benefit obtained (7%), patient decision (3%), and other (9%). The majority of patients (83%) continued chemotherapy beyond documented favorable response, for a mean of 3.1 cycles. Among patients receiving a line of chemotherapy beyond the line of chemotherapy where favorable response was first observed, the mean time from last chemotherapy dose to next line of chemotherapy was 249 days.
Conclusions: Multiple lines of chemotherapy are used to treat metastatic soft tissue sarcoma patients with favorable response to chemotherapy. These data will assist in service planning and evaluation of new therapies for metastatic soft tissue sarcoma patients with favorable response to chemotherapy.

9402 ORAL

Clinical Outcomes of Pelvic Soft-tissue Sarcomas Treated With Surgery and Radiotherapy

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Background: Patients with pelvic soft-tissue sarcomas (PSTS) have an estimated 3-year overall survival (OS) of 60−65%. Patients with PSTS at the Princess Margaret Hospital (PMH) are offered surgery and adjuvant radiotherapy (RT) for the radical management of the disease. This study compares the local recurrence free survival (LRFS), distant metastasis free survival (DMFS), disease free survival (DFS) and OS of patients treated at PMH to historical controls for PSTS and identifies potential prognostic factors.
Material and Methods: Eighty-four patients identified from the PMH cancer registry and electronic patient record with primary (75) or recurrent (9) PSTS received curative treatment with surgery and pre or postoperative radiotherapy to a median dose of 45 Gy. Eleven received neo-adjuvant or adjuvant chemotherapy. Univariate Kaplan–Meier survival and multivariate Cox proportional hazard model analyses were performed. Statistical results are stated as hazard ratios [95% confidence interval]. Variables included in the analysis were: patient age, disease site, size, grade, stage, surgical margin, chemotherapy use and primary vs. recurrent disease. Surgical margins were categorized as positive if the tumour was cut-through or the margin was less than 1 mm with no fascia boundary.
Results: The median follow-up was 3.4 (0.3–11.4) years. The median age at diagnosis was 56. There were 34 uterine and 50 non-uterine PSTS. 67% of the PSTS were high-grade. The 3-year LRFS and OS are 78% and 79% respectively. Multivariate analysis demonstrated that uterine and margin positive PSTS metastasized more frequently: 2.58 [1.67–3.92] and 25 [4.65–1000] respectively. Uterine sarcomas trended towards a shorter OS (p = 0.053). Sub-group multivariate analysis of non-uterine PSTS identified stage (I vs II/III) to be the only significant prognostic factor for LRFS (4.91 [1.22–19.76]) and DFS (3.89 [1.18–12.83]). In uterine PSTS, positive margins were significantly correlated with inferior LRFS (0.204 [0.043–0.981]) and DMFS (0.369 [0.147–0.928]) on multivariate analysis. Stage 1 tumours have a longer OS (4.34 [1.34–13.48]). Positive margins were found in 12.5% of uterine PSTS patients operated at the PMH and 36% when operated in community hospitals. For non-uterine PSTS, 51% of patients operated at PMH and 78% of patients operated in the community have positive margins.
Conclusions: Local control of uterine and non-uterine PSTS are similar, but they differ in their distant relapse rate. Stage is predictive of local and distant disease control in non-uterine PSTS. Achieving a negative surgical margin improves the local and distant control in uterine PSTS, and is better accomplished at centers of excellence in sarcomas. Future research is needed to address stage 2/3 PSTS as these patients are at high risk for local and distant recurrences despite the combined modality treatment approach.

9403 ORAL

Administration of Oncolytic Vaccinia Virus GLV1h68 by Isolated Limb Perfusion to an Immunocompetent Rat Model of Advanced Extremity Sarcoma

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Background: Isolated Limb Perfusion with TNFα and melphalan (TM-ILP) is an established treatment strategy for patients with irresectable extremity sarcoma. Oncolytic viral therapy is in development in clinical trials but has yet to overcome problems inherent in systemic administration. We describe the administration of an oncolytic Vaccinia virus (VV) using a regional technique.
Material and Methods: *In vitro* studies utilising standard colorimetric assays of cell proliferation (MTT) were used to investigate viral efficacy and synergy between VV and melphalan. Live virus was titred using an X-gal stain in a viral plaque assay on CV1 cells. *In vivo* studies were performed in Brown Norway strain rats using the BN175 cell line implanted between the knee and ankle of animals. Perfusion proceeded at the level of the femoral vessels just distal to the inguinal ligament with TNFα, melphalan and virus used alone and in combination.
Results: The virus shows *in vitro* efficacy against a range of human and rat sarcoma and melanoma cell lines. In addition, the virus displays synergy of action with melphalan on combination index analysis. Virus admixed with human blood samples associates predominantly with the cellular component, which may have implications for bioavailability in clinical use. *In vivo*, the combination of virus with TNFα and melphalan resulted in a significant improvement in median survival to humane endpoint over standard TM-ILP (24 vs 16 days, P = 0.01). Biodistribution analysis by qPCR and VPA indicated virus restricted to the perfusion field after ILP, with a 2-log increase in viral DNA copy number at 72hrs suggesting successful viral replication. Work is continuing to establish the role of TNFα in increasing endothelial permeability to the virus as a mechanism for increased efficacy.
Conclusions: Oncolytic viruses can be administered at a high titre by ILP, with minimal systemic spread. They exhibit replication within the tumour and cause growth delay and survival advantage in this rodent model.