8704 ORAL

Adjuvant whole brain radiotherapy versus observation after radiosurgery or surgical resection of 1−3 cerebral metastases - results of the EORTC 22952−26001 study

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Background: The role of prophylactic whole brain radiotherapy (WBRT) after either surgery (S) or radiosurgery (RS) of brain metastases is still debated. The EORTC conducted a phase III trial to define the role of adjuvant WBRT after local treatment (S or RS) of a limited number of brain metastases in solid tumors with stable systemic disease. It was hypothetized that WBRT would increase the duration of functional independence by reducing the number of intracranial relapses.
Material and Methods: Pts eligible for RS had 1−3 metastases of solid tumors (SCLC excluded) $\leqslant$3.5 cm in diameter ($\leqslant$2.5 cm for 2−3 lesions) located outside the brain stem. For S, a complete resection of the metastatic lesions was mandatory. Only pts with absent or stable systemic disease or with asymptomatic primary tumors and in good condition (WHO PS 0−2) were allowed. Pts were randomized to receive either WBRT or observation (OBS). Primary endpoint was survival with functional independence measured by the survival time with WHO PS $\leqslant$ 2. Secondary endpoints were time to intracranial progression, neurologic deaths and overall survival. Analysis is by intent-to-treat (Logrank, two-sided $\alpha = 0.05$).
Results: From 1996 - 2007, 359 pts were recruited, 353 were eligible. Median survival time with WHO PS $\leqslant$ 2 was 10.0 months (95% CI 8.1−11.7) in the OBS arm and 9.5 months (95% CI 7.8−11.9) in the WBRT arm ($p>0.5$). It was only significantly influenced by initial WHO PS and initial systemic disease status ($p < 0.01$). Overall survival was 10.9 months in the OBS and 10.7 months in the WBRT arm ($p>0.5$). Cumulative incidence of intracranial progression at 6 and 24 months was 39.7% (95% CI 32.5−46.8) and 54.2% (95% CI 46.9−61.5) of the OBS pts, but only 15.2% (95% CI 9.9−20.4) and 31.2% (95% CI 24.4−38.0) of the WBRT pts. Both relapses at sites treated initially with S or RS (incidence at 24 months 31.3% vs 16.4%) and at new intracranial sites (32.4 vs 17.6%) were significantly reduced ($p < 0.0001$). Intracranial progression was a cause of the death in 77/179 pts (43%) of the OBS group and in 45/180 pts (25%) of the WBRT group. Median progression-free survival was 3.4 months (95% CI: 3.1−3.9) in the OBS arm and 4.6 months (95% CI: 3.9−6.1) in the WBRT arm ($p < 0.002$).
Conclusions: After radiosurgery or surgery of a limited number of brain metastases, adjuvant whole brain radiotherapy does not prolong the time period of functional independence and overall survival time. Adjuvant whole brain radiotherapy significantly reduces the risk of neurologic death and prolongs progression-free survival.

8705 ORAL

Change in MGMT methylation status between first surgery for newly diagnosed glioblastoma and second surgery for recurrence: clinical implications

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Background: *MGMT* promoter methylation status is a prognostic factor in newly diagnosed glioblastoma patients. However, it is not yet clear whether, and if so how, *MGMT* methylation status may change; nor is it known whether the prognostic role of this epigenetic feature is retained during the disease course.
Methods: A retrospective analysis was made using a database of 614 glioblastoma patients treated prospectively from 01/2000 to 08/2008. We evaluated only patients who met the following inclusion criteria: age $\geqslant$18; PS 0−2; histological diagnosis of glioblastoma at both first and second surgery for recurrence; postoperative treatment consisting of: a) radiotherapy (RT) followed by adjuvant temozolomide (TMZ) until 2005, and b) TMZ concurrent with and adjuvant to RT after 2005; a time interval $\geqslant$3 months between first and second surgery.
Results: *MGMT* status was evaluated at first and second surgery in all 44 patients (M:F 32:12, median age: 49 years, range: 27−67 years). In 38 patients (86.4%) *MGMT* promoter status was assessable at both first and second surgery. *MGMT* methylation status, changed in 37% of second surgery samples and more frequently in methylated than in unmethylated pts (61.5% vs 24%, $p = 0.03$). The median survival was significantly influenced only by *MGMT* methylation status determined at first surgery ($p = 0.04$).
Conclusion: Significant changes in *MGMT* methylation status during the course of GBM occur more frequently in *MGMT* methylated than unmethylated cases. *MGMT* methylation status determined at first surgery appears to be of prognostic value, however it is not predictive of outcome following second surgery.

8706 ORAL

Aggressive management of adult high risk patients with medulloblastoma (MB): 12 years experience at the Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru

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Background: To describe the clinical outcome of adult high risk patients with MB aggressively treated with sequential postoperative external beam radiation therapy (EBRT) and chemotherapy (CHT).
Materials and Methods: We retrospectively collected data from all consecutive adult ($\geqslant$16y) patients treated at our institution for MB from January 1993 to December 2004. High risk patients (according to Chang's Classification) had incomplete surgical resection ($\geqslant$1.5 cm^2 residual) and/or metastases outside the posterior fossa. EBRT delivered 36 Gy at the craniospinal axial level and a boost to 55 Gy in the posterior fossa. CHT consisted mostly of the association of an alkylating agent and a vinca alkaloid for 6 cycles. Survival was calculated from the time of surgery.
Results: Data were retrieved from 78 patients. Median age was 23y (16−51 range). Male/female ratio was 1.2 (43/35). Sixty-four (82%) patients had PS $\leqslant$2. Thirty-three (42%) histologies were desmoplastic. Thirty-seven (47%) patients were classified as high risk: 9 were aggressively treated with both EBRT and CHT, 17 with EBRT alone and 11 received no adjuvant treatment. The groups were homogeneous for clinical pathological characteristics. The association of EBRT followed by CHT yielded a median survival time and a 5y survival rate of 76.9 months (mo) and 75%, respectively. The outcome figures of these patients were significantly better than those of high risk patients not receiving both postoperative treatments (21.2 mo and 6%, RR = 0.19, $p = 0.008$), and comparable to those of patients with standard risk (95.3 mo and 77%, RR = 1.11, $p = 0.867$). Treatment toxicity was mostly mild to moderate and no toxic death was reported.
Conclusions: In our experience, despite the poor prognosis, adult high risk patients with medulloblastoma can display survival outcome comparable to standard risk patients, when treated aggressively. Thus, our findings suggest that, sequential EBRT and CHT are safe and should be proposed, whenever possible, to high risk medulloblastoma patients.

8707 ORAL

Clinical assessment of corticosteroid use and neurocognitive function in patients with glioblastoma at first or second relapse treated with bevacizumab in the BRAIN study

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Background: Patients (pts) with glioblastoma (GBM) can suffer from symptomatic peritumoral edema requiring corticosteroids (CS) and experience neurocognitive decline. We assessed CS use and neurocognitive function (NCF) of pts with recurrent GBM who participated in the BRAIN study (ClinicalTrials.gov NCT00345163).
Material and Methods: BRAIN, a Phase II, open label, multicenter, randomized, noncomparative trial, evaluated efficacy and safety of

bevacizumab (BEV) alone (n = 85) and in combination with irinotecan (IRI) (n = 82) in recurrent GBM. Primary efficacy endpoints were independent review facility-assessed objective response (OR) rate and 6-month (6m) progression-free survival (PFS). CS dosing was captured across time, and pts with an OR were on stable or reduced CS doses. For pts with baseline (BL) CS use, a ⩾50% dose reduction for ⩾50% of time on study drug was a sustained reduction (SR). NCF assessments (memory, visuomotor scanning speed, executive function) were performed at BL and every 6 weeks while on study drug, up to 52 weeks. NCF was categorized as improved, stable, or declined, using the reliable change index. We summarized SR and NCF by response and 6m PFS status.
Results: OR rate (BEV 28.2%, BEV-IRI 37.8%) and 6m PFS (BEV 42.6%, BEV-IRI 50.3%) were compelling. At BL, 50.6% BEV and 52.4% BEV-IRI pts took systemic CS. More than 75% BEV and 65% BEV-IRI pts without CS at BL did not use CS post-BL. Of BEV and BEV-IRI pts with complete or partial response, 57% and 64% had CS SR. Of BEV and BEV-IRI pts with progressive or stable disease, 17% and 38% had CS SR. Of pts with PFS >6m 58% in the BEV arm and 86% in the BEV-IRI arm had CS SR; and of pts with PFS 80%. Of the BEV and BEV-IRI pts with OR, 75.0% and 60.7% had stable or improved performance on all tests at the time of response relative to BL. Of BEV and BEV-IRI pts with PFS >6m, 70.4% and 70.0% had stable or improved performance on all tests at Week 24 relative to BL.
Conclusions: Compared to historical controls, OR rate and 6m PFS in BRAIN were compelling. Most pts with an OR or PFS >6m had decreased CS dose and improved or stable NCF compared to BL. Given the exploratory nature of these analyses in a noncomparative study, these results should be interpreted cautiously.

Poster presentations (Mon, 21 Sep, 09:00−12:00)
Central nervous system

8708 POSTER

Glioblastoma multiforms, long term survivers, single institution experience

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Purpose: Patients with glioblastoma multiforme (GBM) have very poor prognosis; the median survival with the best available treatment is only 12 months. The survival rate has changed little in the past 20 years. This clinico-epidemiological study was prompted to identify specific parameters that might be associated with GBM patients who have achieved an unusual overall survival of >36months post diagnosis.
Patients and Methods: In this clinicoepidemiological study, the frequency of long-term glioblastoma multiforme (GBM) survivors (LTGBMSs) was determined in a population-based study. All patients diagnosed with GBM and referred to Kasr al Aini Center of Radiation Oncology from January 1995 till December 2002 were included in the study. Patients were followed up, and LTGBMSs were defined as GBM patients surviving 3 years or more after diagnosis. Patients were compared in terms of age, sex, and year of diagnosis with standard survivors. Analysis of clinicoepidemiological factors related to survival issues was attempted trying to identify prognostic factors associated with prolonged survival.
Results: One hundred and forty three GBMs patients were diagnosed in the study period; 7 (4.66%) of these patients survived 3 years or more. LTGBMSs (average age, 43.5 years) were significantly younger when compared with all GBM patients (average age, 53.0 years). LTGBMSs had a higher Karnofsky Performance Status score at diagnosis. LTGBMSs were much more likely to have had a gross total resection and adjuvant chemotherapy than the standard GBM patients.
Conclusion: Conventionally treated GBM patients in an unselected population have a very small chance of long-term survival. Aggressive surgical resection as well as adjuvant chemotherapy in addition to sophisticated radiation therapy techniques might contribute to better survival outcome in such dismal disease, particularly in selected patients with young age, good performance status and following near or total resection.

8709 POSTER

What is the value of surveillance scanning in High Grade Glioma?

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Background: Patients with high grade glioma (HGG) often have routine follow up brain scans (CT or MRI) to detect progressive disease. However, the benefit of surveillance scans in this setting is unproven. Here we present data on a cohort of patients with progressive HGG, and analyse whether routine scanning is effective at picking up asymptomatic disease.
Materials and Methods: Chart review of patients with HGG who were diagnosed with progressive disease between 2004 and 2008 in a single cancer centre who were scanned at 6 month intervals after primary treatment. The main outcome documented was whether progression was diagnosed radiologically (on MRI or CT) or clinically. Histology was either anaplastic astrocytoma/oligodendroglioma (G3) or glioblastoma multiforme (GBM). The median age at diagnosis, sex, and time to progression (TTP) from initial diagnosis were also analysed.
Results: 42 patients were identified. 23 had a G3 tumour and 19 had a GBM. The median age at diagnosis was 40 years. 69% of patients were male and 31% female. The majority of patients had clinical progression (76%). Of the 24% who had radiological progression, 40% developed symptoms within a few weeks of the diagnostic scan. 30% never developed symptoms. The remaining 30% developed symptoms months later and were re-scanned. CT brain demonstrated progression in 55% of patients and MRI in 40%. The median TTP was 14 months (22 months in the G3 group and 11 months in the GBM group)
Conclusions: The majority of patients undergoing follow up for a HGG present with symptomatic recurrence. However, 1 in 4 patients in our series had radiologically detected recurrence. In this era of treatment with novel agents, surveillance scans may be appropriate to optimise use of new approaches. A CT brain is adequate to diagnose progression, and represents a cost saving compared to MRI.

8710 POSTER

Improved survivorship of glioblastoma patients treated with combined postoperative radiotherapy and cuncurrent/adjuvant chemotherapy compared to postoperative radiotherapy alone: British Columbia Cancer Agency experience

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Background: After publication of results from the EORTC-NCIC CE3 randomized study showing improved survival with the addition of concurrent/adjuvant temozolomide (TMZ) to postoperative radiotherapy (PRT) for treatment of glioblastoma (GBM), use of TMZ became standard practice at the British Columbia Cancer Agency (BCCA). PCV and CCNU chemotherapy (ChT) used prior to that report were not consistent. This study aimed to verify that addition of TMZ to PRT is associated with better outcome in patients with GBM in a general population setting. The BCCA provides all radiotherapy services to a population of 4 million in a distinct geographic area.
Material and Methods: Between 01/01/2000 and 30/06/06 a total of 376 patients with histologically confirmed GBM of 19−70 years of age and ECOG performance status 0−2 (selection criteria for EORTC-NCIC trial eligibility), were treated with radical PRT to the total dose of 40−60 Gy. Of these 136 received concurrent/adjuvant TMZ and 59 received non-TMZ ChT. The primary end point was overall survival.
Results: The two-year overall survival of the entire cohort was 20.6%. Follow-up was sufficient to capture 92% of the events. The two-year survival was 8.9% in PRT alone, 31.6% in TMZ, and 30.5% in non-TMZ ChT subgroups, i.e. statistically different between PRT alone and any ChT subgroups (Logrank $p < 0.0001$), but no different between TMZ and non-TMZ ChT subgroups. The two-year survival was highest for patients who received 60 Gy of PRT combined with TMZ or non-TMZ ChT (37.1% and 36.4% respectively). Multivariate analysis showed use of any concurrent/adjuvant ChT, dose of PRT (60 Gy vs. less than 60 Gy) and younger age at diagnosis were independent predictors of better overall survival.
Conclusions: Amongst a population-based patient cohort similar to that of the EORTC-NCIC CE3 trial, addition of ChT to PRT was associated with better overall survival, similar to results from the trial. This study showed that results from the protocol can be translated successfully to population use outside the confines of the randomized trial setting.