Conclusion: Chemotherapy given after postoperative radiotherapy in patients with oligodendroglioma did not improve survival in this retrospective study.

520 PUBLICATION

Analysis of prognostic factors in patients with glioblastoma multiforme treated with postoperative radiotherapy

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Purpose: To evaluate prognostic factors of patients with Glioblastoma multiforme (GBM) treated with postoperative radiotherapy (RT).
Materials and methods: Between October 1995 and December 2003, 80 patients with newly diagnosed GBM were treated with postoperative RT at our department. Patients were assigned to RPA groups. We also evaluated several potential prognostic factors for survival. The influence of various factors of age, sex, Karnofsky performance status (KPS), histology, a history of seizure at diagnosis, type of surgery, RT dose, median waiting time from operation to RT, median duration of RT, duration of symptoms, presence of chemotherapy, initial tumor size, postoperative tumor size, neurologic status of preoperative, postoperative and after RT, family history of cancer and RPA groups on overall survival were studied. The Kaplan-Meier method, Log-rank test and the Cox proportional hazard model were used for statistical analysis.
Results: All patients evaluated in April 2005. Median follow-up was 8 months (1–37 months) and 89 patients died at analysis time. Median age was 55 years (20–73 years) with 49 male and 31 female patients. Surgical treatment consisted of biopsy, subtotal resection and total resection of 16, 39 and 25 patients, respectively. All patients had received eksternal beam radiotherapy with a median dose of 60 Gy (22–66 Gy). In 2 cases (2.5%) the tumor was multicentric. The median waiting time from operation to RT was 20 days (1–54 days) and the median duration of RT was 42 days (15–71 days). A total of 33 patients received adjuvant or concurrent chemotherapy with RT. The overall median survival was 8 months (1–37 months) for the total group and 15, 8, 9 and 3 months for RPA group III (n = 12), IV (n = 35), V (n = 29) and VI (n = 4), respectively. The 1, 2 and 3 year overall survival rate were 31%, 5% and 2%, respectively. The following parameters were significantly associated with prolonged survival:
1. KPS of 80 or more (10 and 4 months, $P < 0.001$)
2. total tumor resection (13 and 7 months, $P < 0.001$)
3. total dose of RT (<60 Gy vs *60 Gy; 3 and 9 months, $P < 0.001$)
4. initial tumor size ($\leqslant$4 vs >4 cm; 9 and 8 months, $P < 0.001$)
5. absence of neurologic defisite after surgery (10 and 6 months, $p < 0.001$)
6. absence of neurologic defisite after RT (11 and 5 months, $p < 0.001$) and RPA groups ($p < 0.05$).

Conclusion: Glioblastoma multiforme remains an important cause of morbidity and mortality from intracranial tumors. Karnofsky performance status, total tumor resection, total dose of RT, initial tumor size, absence of neurologic defisite and RPA grops are prognostic factors for predicting survival of GBM patients.

521 PUBLICATION

Radiosensitized treatment of different brain tumors with hematoporphyrin derivative

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Background: While primary malignant brain tumors account for only 2% of all adult cancers, these neoplasms cause a high amount of cancer-related deaths. The incidence of primary brain tumors is increasing, so the emergence of novel treatment methods for these tumors has led to heightened interest. High level of porphyrins is noticed in glioma tissue, therefore sensitized gliomas treatment is hopeful. Our hypothesis was that the some of the rays who can provide ionizing radiation (x-rays and/or gamma rays) could activate some of hematoporphyrin derivatives (HpD). To prove it, we have performed experiments on mice and rats. A favourable outcome of our animal experimental study has encouraged us to utilize radiosensitized treatment (RST) in Lithuanian Oncology Center in 1989. The purpose of this work was to investigate and to enlarge the possibilities of sensitized brain tumors treatment using some HpD as radiosensitizer.
Materials and methods: Since 1998 03 the total of 89 patients with advanced primary or metastatical brain tumors underwent RST as palliation. There were 58 patients with primary malignant tumors and 27 patients with with solitary metastatic brain tumors (16 patients) or with tumors, which were grown into the brain from the surrounding tissue (11 patients). There were 4 patients with primary benign tumors too. Tumors were irradiated with gamma rays 2 Gy at a time from radioactive 60Co 24, 48 and 72 h after injection i.v. of the HpD (the full dose of the course was 6 Gy). 23 patients underwent a single course of RST, for the rest RST was repeated. CT- and /or MRI-examination was provided for all patients before the treatment and 1–1.5 mo. after each RST course.
Results: As the immediate result of RST of malignant brain tumors, 31 malignances (in 14 patients) fully disappeared. However the recurrent disease was noticed in 4 of them after 49; 37; 24 and 6 mo. The significant response – the regression of tumor and remission of the disease for more than 6 mo. – was observed in 24 patients. Partial response was noticed in 25 patients. For the rest patients the treatment was ineffective. RST was ineffective for all patients with benign brain tumors.
Conclusions: RST is a new and effective method of treatment in malignant brain tumors both primary and metastatical. The effectiveness of RST depends on the morphological type of tumor.

522 PUBLICATION

Therapeutic results in patients with anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM) receiving postoperative radiotherapy and concomitant temozolomide

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Background: We retrospectively evaluate our therapeutic results in patients with anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM) receiving postoperative radiotherapy and concomitant temozolomide.
Materials and method: The medical records of 32 patients treated by postoperative external beam radiotherapy (RT) and concomitant temozolomide chemotherapy at our institution were analyzed. Karnofsky performance score (KPS) was above 70 in all patients. There were 10 female and 22 male patients with a median age of 49 years (range, 21–53 years). Histopathology was GBM in 25 and AA in 7 patients. Subtotal excision was performed in 19 and gross total excision in 12 patients. Three patients were treated with an accelerated fractionation scheme (1.5 Gy bid to a total dose of 45 Gy), while 29 patients were treated with conventional scheme (2 Gy daily to a total dose of 60 Gy). Initial radiotherapy portals included primary tumor volume plus 3 cm, and boost volume included primary tumor plus 1 cm. Localization was performed after 40.5 Gy for accelerated scheme and after 40 Gy for conventional scheme. Temozolomide was given in 100 mg/m^2 doses (PO once daily, max. dose 200 mg), during the first and the third week of RT course in 17 patients. Since this dosage was well tolerated, we increased dosage to 150 mg/m^2 ((PO once daily, max. dose 300 mg)in last 15 patients. Informed consent was obtained from all patients before the start of therapy.
Results: The median follow-up was 10 months (range 3–17 months). Nineteen patients had either no evidence of disease or stabile disease, while progression was observed in 7 patients at last follow-up. Six patients died of disease. The median overall survival was 15 months (17 months for AA, and 14 months for GBM, $p = 0.06$). Patients with gross total excision had better overall survival than patients with subtotal excision (17 months vs. 13 months, $p = 0.05$) in univariate analyses. Gender, age, KPS, type of surgery, grade, and RT scheme were analyzed as prognostic factors in multivariate analysis, and no significant factor affecting the overall survival was found. Emesis was the predominant toxicity during treatment observed in 9 patients (28%). Skin toxicity due to drug reaction were seen in 2 patients. But both receied phenytoin with temozolamide. No other serious acute and late toxicity was noted due to either RT or temozolomide.
Discussion: Postoperative radiotherapy and concomitant temozolomide seems to be an effective and safe treatment regimen for patients with AA and GBM.

523 PUBLICATION

Temozolomide in the treatment of high grade gliomas

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Purpose: to present the results obtained in treatment of primary high grade gliomas with postoperative radiotherapy and chemotherapy with Temozlomide, the toxicity and the compliance to treatment.
Material and methods: We treated 61 patients between 1999–2004. The median age was 41 years (10 and 64 years old). Histology: 30 patients with glioblastoma multiforme, 23 patients with anaplastic astrocytoma and 8 patients with anaplastic oligoastrocitoma. The standard treatment was surgery followed by radiotherapy. There were 39 patients with macroscopic total resection and 22 with partial resection. Postoperative radiotherapy consisted in focal irradiation in daily fractions of 1.8–2 Gy/5 days per week

for 5 –6 weeks for a total dose of 50–60 Gy. Chemotherapy with Temozolomide was delivered concomitant with radiotherapy (75 mg/sqm/d × 7 d/wk) followed by six cycles of adjuvant temozolomide (200 mg/sqm/d × 5 days, every 28 days) in 21 patients. Adjuvant Temozolomide (200 mg/sqm/d × 5 days, every 28 days) was delivered after three weeks from the radiotherapy to 30 patients and to 9 patients with relapse after radiotherapy with curative intent.
Results: Concomitant Temozolomide with RT+ adjuvant TMZ was followed by 5 partial responses, 8 stable diseases, 14 patients were free of disease three month after completion of treatment and 3 patients with progressive disease. For patients with Temozolomide adjuvant to RT we obtained 3 partial responses, 12 stable disease, 1 patient with progressive disease and 5 patients were free of disease. Median survival was 13 months for patients with concomitant treatment, and 6.5 months for patients with adjuvant treatment. The main toxicities were: grade 1 and 2 nausea and vomiting in 12 patients, grade 2 trombocytopenia in 6 patients, grade 3 skin toxicity in 2 patients and obstipation in 7 patients.
Conclusion: Combined radiotherapy and Temozolomide, for high-grade gliomas, concomitant or adjuvant, is feasible with acceptable toxicities and good compliance. This protocol may prolong the disease free interval and possible the survival of patients with high-grade gliomas.

524 PUBLICATION

Concomitant radio-chemotherapy with temozolomide in malignant gliomas

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Background: Malignant gliomas are highly aggressive tumors with frequent relapse after surgery and no effective treatment at this time. In our study we assess the efficacy of concomitant radiotherapy and temozolomide in multiform glioblastoma treatment.
Patients and methods: Between June 2002-June 2003 12 patients have been treated after optimal surgery for glioblastoma multiforme. Median age was 48 years (range 39–60 years). Sex ratio male/female was 2:1. Treatment schedule was: external radiotherapy up to 60 Gy, in the target volume, conventional fractionation 30 × 200 cGy 6 weeks and Temozolomide: 150 mg/m^2/day, days 8–12 and 36–40, concomitant with RT followed by 6 more cycles with Temozolomide 200 mg/m^2/day, days 1–5, repeated at 28 days.
Results: Haematological toxicity was grade 3 leucopenia 2 patients, grade 3 anemia 1 patient and grade 3 trombocitopenia 1 patient, no grade 4 toxicity. Nonhaematological toxicity: fatigability grade 1–2 in 4 patients, grade 3–4 in 1 patient, rash grade 1–2 in 2 patients, grade 3–4 in 1 patient, nausea grade 1–2 in 4 patients, grade 3–4 in 1 patient. Median survival was 16.5 months; 8 patients are alive after 1 year (6 of them free of disease) and free of disease median survival was 7.8 months.
Conclusions: The treatment scheme has been well tolerated. Results are slightly better than those with postoperative RT alone and are similar to those reported in other studies or with daily administration (50–75 mg/m^2/day for 6 weeks). Further investigation is required.

525 PUBLICATION

The effect of a tumour board on the prognosis of patients with brain metastases treated using radiosurgery

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Purpose: To analyse prognostic factors and classification schemes for patients with brain metastases selected by a tumour board for stereotactic radiosurgery (SRS).
Materials and methods: From June 1997 to December 2004, 69 patients with 1–3 brain metastases received SRS, most as a boost after 30 Gy/10 whole brain radiotherapy (WBRT), and some as salvage after craniotomy and/or 20 Gy/5 WBRT. Twenty-six patients had lung, 17 had breast, and 26 had other histologies. The largest lesion per patient had a median diameter of 20 mm (3–31). The patients had a median age of 56 (35–78) and a median ECOG-PS of 1 (0–3). A median dose of 18 Gy (13.5–24) was prescribed to the 80% isodose surface. For each patient, the RTOG recursive partitioning analysis class (RPA), score index for radiosurgery in brain metastasis (SIR), and the basic score for brain metastasis (BS-BM) were determined.
Results: For the entire cohort, the median survival was 12.0 months, and univariate Cox regression of age, KPS, ECOG-PS, Lesion Number, Lesion Volume, Primary Control, Extra-cranial Metastases, Histology, RPA, SIR, and BS-BM determined that only younger Age ($p = 0.003$) predicted for better survival. For the subset that excluded the 3 outlying patients with survival >36 months, the median survival was also 12.0 months. In this subset, univariate Cox regression demonstrated that younger Age ($p = 0.009$), better ECOG-PS ($p = 0.001$) and, unexpectedly, higher Lesion Number ($p = 0.01$) predicted for better survival. Multivariate Cox regression determined that younger Age ($p = 0.045$) and better ECOG-PS ($p = 0.01$) predicted for better survival.
Conclusions: For this cohort of patients with brain metastases, selected for radiosurgery by a tumour board, the median survival compared favourably with other reports; however, RPA class, BS-BM and SIR did not predict for patient survival. Patients with fewer lesions had a significantly poorer survival than those with more lesions, suggesting that the tumour board exerted selection pressure, altering the usual influence of known prognostic factors in this cohort.

526 PUBLICATION

The role of age for survival in high grade glial tumors

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Purpose: In this retrospective study we analyzed the results of radiotherapy in patients with surgically removed high grade brain tumors treated with postoperative radiotherapy (RT).
Materials and methods: Between July 1999 and December 2004, 53 patients (28 male, 25 female) were treated in our department. Median age of the patients was 52 (18–75) years. Seven patients had a total surgical resection, 30 near total resection, and 14 subtotal resection. In 2 patients, diagnosis was based upon clinical and radiological data. The pathology was consistent with grade III astrocytoma in 12 (22.6%) and glioblastoma multiforme in 41 (77.4%) patients. At the time of diagnosis 21 (39.6%) patients had ⩽ 70 karnofsky performance status and 10 (19%) had history of seizure. Adjuvant RT was given with a single daily fraction of 1.8 Gy to a total dose of 63 Gy. The median interval between surgery and radiotherapy (RT) was 37 days and RT was completed in median 49 days. Twenty-eight (52.8%) patients received chemotherapy after completion of RT for this study, the prognostic importance of age, sex, performance status, a history of seizure at diagnosis, extent of surgery for overall survival were analyzed. Mean follow-up period was 15 (2–64) months.
Results: The median overall survival was 25 months. Fourteen patients are alive without any recurrence. More than 50 years of age was the only significant factor in univariate analysis and there were no significant factors in multivariate analysis for overall survival.
Conclusion: This study concluded that more than 50 years of age was a poor prognostic factor in glioblastoma multiforme.

Clinical Trials Methodology and Ethics

Poster presentations (Wed, 2 Nov)
Clinical trials methodology and ethics

527 POSTER

Impact of the new European regulation on the authorisation of new oncology drugs in the European Union (EU)

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On 20 November 2005, new European pharmaceutical legislation will enter into force. Thereafter, all oncology drugs seeking approval in the EU will be evaluated *via* the European Medicines Agency (EMEA) leading to an EU-wide approval. This review focuses on the main regulatory changes related to the centralized procedure and the new concepts for approval that may affect applications for oncology products.
Regulation (EC) No. 726/2004 introduces new tools and procedures allowing early access to new drugs, including anticancer drugs. One of theses measures is the 150 days accelerated procedure (instead of 210 days) for drugs that are of major public health interest, particularly in terms of therapeutic innovation. Moreover, renewable conditional authorisations may be granted for certain products pending completion of further studies (detailed implementing legislation is expected to be adopted by the time of reporting). The existing mechanism of approval under exceptional circumstances when the rarity of the indication, the state of the scientific knowledge or the principles of medical ethic do not allow to provide