Concurrent Chemo-Radiotherapy in Treatment of Brain Secondries

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Abstract: Background: Brain metastases are the most common cause of intracranial mass lesions. As primary cancer treatments such as surgery, radiation therapy and chemotherapy have become more effective in the past few decades, people with cancer are living longer after initial treatment than ever before. Treatment efficacy is determined by the sensitivity of tumor cells to chemotherapeutic agents and whether or not these drugs can cross the blood brain barrier (BBB). The present study evaluated the efficacy and toxicity of gemcitabine given concurrently with whole brain radiation therapy in patients with brain metastases. **Patients & Methods:** This is a phase II prospective study included 50 patients with radiologically proven brain secondries of pathologically proven primary solid tumor, who presented to Clinical Oncology Department, Assiut University Hospital from November 2004 to October 2006. Each patient was subjected to medical decompression, and was given palliative whole brain irradiation aiming at 30 Gy/10 fractions/2 weeks with gemcitabine 50 mg/ m2 weekly by 30 minutes IV infusion. **Results:** With mean age of 59.71 years, (23; 46.0%) were male patients, with distribution of ECOG PS was (14 patients; 28.0%) in grade 1, (30 patients; 60.0%) in grade 2 and (6 patients; 12.0%) in grade 3. Regarding response to treatment, one patient (2.0%) had complete response, 3 patients (6.0%) had partial response, 18 patients (36.0%) had stable disease and 28 patients (56.0%) had progressive diseases. The median PFS was 9 months and OS was 14 months. All patients tolerated treatment regimen well with only two patients (4%) suffered from grade 2 thrombocytopenia. **Conclusions:** Gemcitabine based concurrent chemo-radiation with 50 mg/ m2 weekly resulted in favorable response rate, and satisfactory median PFS and OS with accepted toxicity profile.

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1. Introduction

Brain metastases (BM) are by far the most frequent intracranial tumor in adults, outnumbering primary brain tumors by about four times (1).

However, brain metastases still occur in many patients months or even years after their original cancer treatment. Brain metastases have a poor prognosis for cure, but modern treatments are allowing patients to live months and sometimes years after the diagnosis (2, 3).

In the younger age groups, sarcomas (osteogenic and Ewing's) and germ cell tumors are more common. Renal, colon and breast carcinomas generally produce single metastases whereas malignant melanoma and lung generally produce multiple secondary brain lesions (4).

The evidence of the efficacy of gemcitabine to inhibit the growth of human neoplasms was obtained in a broad range of solid and hematological cancer cell lines, as well as in in vivo murine solid tumors and human tumor xenografts in nude mice. Consequently gemcitabine was extensively studied in a variety of tumors in which significant clinical activity has been reported. Today gemcitabine is indicated as a single agent in the treatment of patients with metastatic pancreatic cancer and in combination chemotherapy in non-small cell lung cancer, bladder cancer and breast cancer (5).

The present study evaluated the efficacy and toxicity profile of gemcitabine given concurrently with whole brain radiation therapy in patients with brain metastases.

2. Patients and Methods

This is a phase II prospective study included 50 patients with radiologically proven brain secondries of pathologically proven primary solid tumor, who presented to Clinical Oncology Department, Assiut University Hospital from November 2004 to October 2006.

Eligibility Criteria:

1- Patients with radiologically proven brain secondries of pathologically proven primary solid tumor.

2- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3.

3- No pulmonary or cardiovascular contraindications.

4- Adequate hematological, hepatic and renal functions.

5- Patients given written informed consent.

Treatment Plan:

Every patient in this study had been subjected to the following:

1-Medical treatment:

A- Medical decompression in the form of steroids and diuretics.

B- Anticonvulsants if indicated.

2-Radiotherapy:

a) Target volume: whole brain.

b) Localization:

-Tumor localization was done using simulator (Toshiba®).

-The patient lies supine with arm adducted.

- Fixation by head holder and an immobilizing thermoplastic mask.

- Lateral simulator films were taken and field margins chosen to cover the target volume.

-The center of the field is marked on the patient and IPD is measured at this point.

c) Fields arrangement: Two parallel opposing fields were used to cover the whole brain with sparing of both eye globes.

d) Dose and machines: 30 Gy in 10 fractions over 2 weeks were given to each patient. All patients are treated by linear accelerator 6 MV or by Cobalt 60 machine.

3- Chemotherapy: Gemcitabine; 50 mg/ m2 was given in 250 ml NS 0.9%, to each patient by 30 minutes IV infusion on weekly basis before radiation sittings.

Statistical analysis

The outcome measurements of this treatment included response rate, progression free survival (PFS) and overall survival (OS). PFS was calculated from the date of induction chemotherapy to the documented date of progression or date of death from any cause. OS was defined as the time from the start of induction chemotherapy to death from any cause. The median PFS and OS were estimated with the Kaplan-Meier method. The X2 test and Fisher's exact test were used to test the correlation between treatment outcomes and prognostic factors as age, sex, T and N stage, overall stage, primary tumor site, and smoking and performance status.

3. Results

With mean age of 59.71 years, (23; 46.0%) were male patients, with distribution of ECOG PS was 14 patients (28.0%) in grade 1, 30 patients (60.0%) in grade 2 and 6 patients (12.0%) in grade 3. Regarding primary tumor site, there were 22 patients (44.0%) had breast cancer, 18 patients (36.0%) had lung cancer, 6 patients (12.0%) had MUO (Metastasis of Unknown Origin), 2 patients (4.0%) had renal cell carcinoma and 2 patients (4.0%) had colo-rectal carcinoma. Regarding extent of metastases, there were 7 patients (14.0%) had limited "1-3 lesions", and 43 (86.0%) had multiple ">3 lesions" [table 1]. The majority of female patients had breast cancer (22 out of 27; 81.5%), while most of male patients had lung cancer (15 out of 23; 65.2%). There were 4 out of 23 male patients (17.4%) had MUO whereas 2 out of 27 female patients (7.4%) had MUO [table 2]. Regarding treatment related response rate, only one patient (2.0%) had CR, 3 patients (6.0%) had PR, 18 patients (36.0%) had SD and 28 patients (56.0%) had PD [figure 1]. With median follow up period of 16 months, the median PFS was 9 months (with mean value of 9.57±2.27 months) whereas the median OS was 14 months (with mean value of 15.25 ± 4.04 months). The majority of cases (N=34; 68%) died during the period of study assessment [table 3, figures 2 & 3]. All patients had tolerated treatment regimen well with only two patients (4%) suffered from grade 2 thrombocytopenia that did not result in treatment interruption. Our results showed that treatment protocol resulted in significant improvement (P<0.001) of neurological function [table 4].

Table (1): Characteristic data in study group

Item	"Gem+RT" "n=50"
1-Age "years"	
Mean ± S.D	59.71 ± 9.29
(min-max)	(29.0-78.0)
Median	60
2-Sex:	
• Male	23(46.0%)
• female	27(54.0%)
3-ECOG PS:	
1	14(28.0%)
2	30(60.0%)
3	6 (12.0%)
5- Primary tumor site:	
Breast cancer	22 (44.0%)
Lung cancer	18(36.0%)
MUO(Metastasis of Unknown Origin)	6(12.0%)
Renal cell carcinoma	2(4.0%)
Colo-Rectal carcinoma	2(4.0%)
6-Brain metastases:	
• Limited "1-3lesions"	7(14.0%)
• Multiple">3 lesions"	43 (86.0%)

Table (2): Relation between diagnosis and gender in study group.

Diagnosis	Male	Female	Total
Breast Cancer	0	22(81.5%)	22(44.0%)
Lung cancer	15(65.2%)	3(11.1%)	18(36.0%)
MUO(Metastasis of Unknown Origin)	4(17.4%)	2(7.4%)	6(12.0%)
Renal Cell Carcinoma	2(8.7%)	0	2(4.0%)
Colo-Rectal Carcinoma	2(8.7%)	0	2(4.0%)
Total	**23(46.0%)**	**27(54.0%)**	**50**

Table (3): Outcome and overall survival and progression free survival.

Item	Group "Gem+RT" "n=50"
1-Out come:	
Death	34 (68.0%)
Living	16 (32.0%)
2-P.F.S	
Mean ± S.D	9.57 ± 2.27
(min-max)	(7.0-14.0)
Median	9
3-O.S:	
Mean ± S.D	15.25 ± 4.04
(min-max)	(8.0-28.0)
Median	14

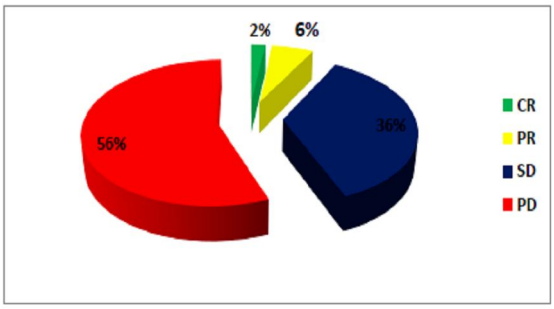

Fig (1): Response in study group.

Table (4): Relation between Neurological function statuses in study group.

Item	Neurological function status			
	Level I	Level II	Level III	p-value
• baseline	12(24.0%)	28(56.0%)	10(20.0%)	
• post	22(44.0%)	22(44.0%)	6(12.0%)	P<0.001**

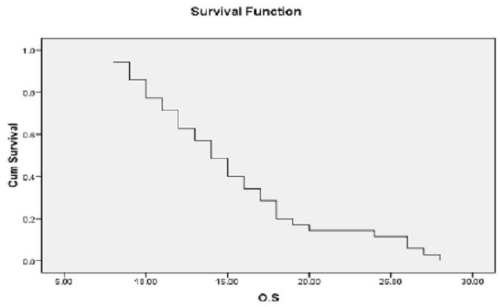

Fig (2): Overall survival in study group

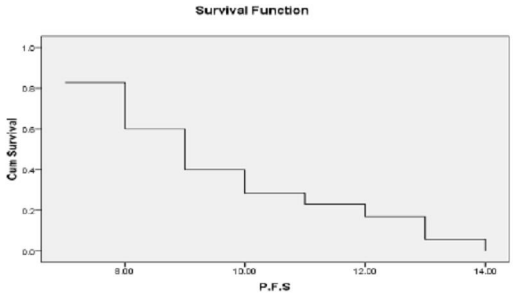

Fig (3): P.F.S in study group

4. Discussion

The standard treatment of patients with multiple brain metastases is whole brain irradiation that results in transit response in most of patients (6), and leads to delay the progression of neurologic deficits and decrease steroid dependency (7).

A strategy to improve the local dose intensification of radiation is the use of systemic agents, such as chemotherapy agents, to augment the efficacy of irradiation. The combination of radiotherapy and chemotherapy is advocated primarily because of the independent effects of each modality (8).

Chemo-radiation using previous regimens showed no difference in the overall response rates or median survival time. The studies however suggested that chemo-radiation is feasible, myelo-suppression being the only important toxicity. On the other hand, Gemcitabine has shown a clear potent efficacy in different solid tumors, including non-small cell lung cancer (NSCLC), small cell lung cancer, head and neck squamous cell cancer, germ cell tumors, and tumors of the bladder, breast, ovary, cervix, pancreas, and biliary tract (9 & 10). In addition to its cytotoxic effect, gemcitabine is a potent radio-sensitizer both in vitro and in vivo (11, & 12) as it is believed to cross the disrupted blood-brain barrier.

The radio-sensitization of gemcitabine usually occurs under conditions where cancer cell lines demonstrate a concurrent redistribution in S phase of cell cycle (13 & 14) and may be due to apoptosis (14).

Therefore, the present study used gemcitabine concurrently with whole brain radiation therapy in patients with brain metastases.

Present study showed that the commonest primary was breast cancer (44%), followed by lung cancer (36%) and renal cell carcinoma (4%). In the reported literature, the five cancers that associate with brain metastases include breast cancer (25-30%), lung cancer (22-25%), and renal cell carcinoma (<5%). This is confirmed by a study conducted by Subramanian et al. (2002) (4). where the commonest primary tumor resulting in brain metastases, is lung, followed by breast, skin and colon.

The primary end point in our study was to assess treatment related toxicity. Fortunately, the treatment regimen used in this study was tolerable, as only two patients (4%) suffered from grade 2 thrombocytopenia that did not result in treatment interruption. This favorable toxicity profile may be explained by the low dose of Gemcitabine (50 mg/ m2) used concurrently with irradiation on weekly basis. However, reported studies showed a wide range (0- 20%) of grade 2-4 thrombocytopenia because of using larger doses of Gemcitabine (15).

In a phase I study conducted by Maraveyas et al., (16), who addressed the maximum tolerated dose of gemcitabine as a radio-sensitiser for the treatment of patients with brain metastases, it was found that the MTD of Gemcitabine at this schedule in patients with BM is 62.5mg/ m2.

The secondary end points in the present study were evaluation of response to treatment as well as estimation of overall survival rate. Patients' characteristics in the present study showed that the majority of our patients had unfavorable criteria, such as poor ECOG performance status (score 2 & 3; 72%), multiple brain metastases (>3; 86%), and of intrinsically radio-resistant primaries (breast cancer, NSCLC, renal, and colorectal carcinomas). Although these unfavorable patient and tumor related criteria, the treatment regimen used in the current study yielded a satisfactory outcome. At the time of analysis, the response rate to the used treatment regimen in our study was 44% (22 out of 50 cases) and included patients who achieved CR (n=1; 2%), PR (n=3; 6%) and SD (n=18; 36). The majority of cases (68%) died during the period of study assessment, with median PFS was 9 months and median OS was 14 months. This is comparable with a study reported by Maraveyas et al., (16) who found 40% response rate to whole brain irradiation with concurrent Gemcitabine. The reported study also found that 14 cases (56%) died within 6 months.

Most reported studies (17) that addressed Gemcitabine based chemo-radiation showed median overall survival rates ranged from 5.5 to 10 months. These results are lower than our findings that could be due to predominance of NSCLC primaries in the reported studies. Furthermore, the used treatment regimen in the current study, resulted in statistically significant improvement of neurological function ($p<0.001$). This is in agreement with most of the reported studies (18) where WBRT improves neurologic symptoms.

Conclusions

Gemcitabine based concurrent chemo-radiation with 50 mg/ m2 weekly resulted in favorable response rate, improved neurological function as well as satisfactory median PFS and OS with accepted toxicity profile.

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