The treatment of patients who have experienced intracranial progression of brain metastases after whole brain radiation therapy (WBRT) is a clinical challenge. The purpose of our retrospective study is to describe the clinical outcomes of the application of linear-quadratic model in reirradiation of brain metastases (M1BRA) and to present the experience of Radiotherapy Department – Sf. Ap. Andrei Emergency Clinical Hospital, Galati with respect to the re-irradiation of patients with progressive or recurrent brain metastatic disease after initial WBRT. Between January 2006 and December 2013, 43 patients were treated with WBRT for brain metastases and retreated with WBRT at a later date. The median age was 58 years old. The most common primary sites were lung (46.51% of cases) and breast (16.28% of patients). The most frequent dose used for the initial radiotherapy was 30Gy/10 fractions (72.09% of patients). The most common fractionation schema of re-irradiation was 20Gy/10 fractions (67.44% patients). Thirty per cent of patients experienced a complete clinical response after re-irradiation, 33% had partial response, 22% remained stable; 15% manifested progression of disease after re-irradiation.

Key words: linear quadratic-model, brain metastases, radiotherapy.

1. INTRODUCTION

Brain metastasis occur in 25–45% of cancer patients and present a poor prognosis, median survival rate is 1–2 months with best supportive care. Systemic treatments are continuously improved, consequently cancer death rates are decreasing and patients with metastatic disease are living longer [1]. In case of multiple brain metastases (M1BRA), the median survival rate is between 3 and 6 months. The therapeutic options for patients with brain metastases are: surgery, stereotactic radiotherapy and external beam radiotherapy [2]. Whole brain radiotherapy (WBRT) is the most common treatment modality for M1BRA, has an effect on palliation and stabilizing cranial progression and it increases survival [1].
Re-irradiation of secondary brain lesions can improve the patient’s quality of life and increase his chances of survival. In case of M1BRA patients who previously performed WBRT, the therapeutic options are: stereotactic radiotherapy, surgery, chemotherapy, WBRT (second course), steroids or best supportive care and it depends on number and localization of M1BRA, primary tumors type, extracranial disease extension and life expectancy [2, 3].

The main goals of radiotherapy are to control the neurological symptoms, decrease the steroids administration and to improve the quality of life.

The brain tolerance to reirradiation depends on previous total dose (TD), fractionations schemas, entirely treated tumor volume, and time interval between two radiotherapy courses [4].

2. METHOD AND MATERIAL

Our retrospective study analyzed 43 patients with brain metastases who performed reirradiation on secondary bone lesions, between January 1st 2006 and December 31st 2013 in The Sf. Ap. Andrei Emergency Clinical Hospital, Galati, Radiotherapy and Oncology Department. These 43 patients represent 19.2% out of a total of 224 brain metastases patients with different primary sites, who performed radiotherapy in the same period. The following parameters were analyzed: site of primary tumor, fractionation schemas used during the first and second irradiation, symptoms control (Tables 1, 2) and survival rates.

Median age was 58 years old (range 31–75 years), 60.47% were men and 39.53% were women.

The primary site distribution was as it follows: lung (non-small cell) – 15 (32.56%), lung (small cell) – 6 (13.95%), breast 7 (16.28%), melanoma – 2 (4.65%), renal 3 (6.98%), colorectal 3 (6.98%), bladder – 1 (2.33%), lymphoma – 2 (4.65%) and endometrium – 1 (2%).

Fractionation schemas for reirradiation were stated according to linear quadratic-model. The parameters are: $\alpha/\beta$ report, previous total doses and previous dose per fraction, biological effective dose (BED), time interval between the two irradiations and patient’s performance status.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients (%)</th>
<th>N = 43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) median (range)</td>
<td>58 (31–75)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (60.47)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17 (39.53)</td>
<td></td>
</tr>
</tbody>
</table>
Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) median (range)</td>
<td>58 (31–75)</td>
</tr>
<tr>
<td><strong>Primary tumor site</strong></td>
<td></td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>6 (13.95)</td>
</tr>
<tr>
<td>Non-small cell cancer</td>
<td>14 (32.56)</td>
</tr>
<tr>
<td>Breast</td>
<td>7 (16.28)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>2 (4.65)</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (6.98)</td>
</tr>
<tr>
<td>Bladder</td>
<td>1 (2.33)</td>
</tr>
<tr>
<td>Testicular</td>
<td>2 (4.65)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>3 (6.98)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2 (4.65)</td>
</tr>
<tr>
<td>Cervix</td>
<td>2 (4.65)</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1 (2.33)</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Fractionation schemas at first irradiation</th>
<th>No. of patients (%)</th>
<th>Fractionation schemas at re-irradiation</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD = 30Gy/10fractions/10 days, d/fr. = 3Gy, α/β = 3Gy; BED = 60Gy</td>
<td>31 (72.09)</td>
<td>TD = 15Gy/5fractions/5 days, d/fr. = 3 Gy, α/β = 3Gy, BED = 30 Gy</td>
<td>13 (30.23)</td>
</tr>
<tr>
<td>TD = 20Gy/5fractions/5–7 days, d/fr. = 4Gy, α/β = 3Gy; BED = 46.6 Gy</td>
<td>12 (27.91)</td>
<td>TD = 20Gy/10fractions/10 days, d/fr. = 2 Gy, α/β = 3Gy, BED = 33.2 Gy</td>
<td>29 (67.44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TD = 12 Gy/3fractions/3 days, d/fr. = 4 Gy, α/β = 3Gy, BED = 28 Gy</td>
<td>1 (2.33)</td>
</tr>
</tbody>
</table>

We calculated the BED for each re-irradiation case according to the formulae (1) and (2). BED measures the effect of a fractionated or continuous radiotherapy; having the units of dose, it is expressed in grays (Gy) [5, 6, 7].

\[
BED = TD \cdot \left(1 + \frac{d}{\alpha/\beta}\right), \tag{1}
\]

\[
TD = nd, \tag{2}
\]
where:

\[ n = \text{fraction number}; \]
\[ d = \text{dose per fraction}; \]
\[ \text{BED} = \text{biological effective dose}; \]
\[ \text{TD} = \text{total dose}; \]
\[ \alpha/\beta = \text{ratio for each concerning tissue.} \]

We chose \( \alpha/\beta \) for normal brain tissue 3Gy [6, 7].

At first irradiation, the fractionation schemas were TD = 30Gy/10fractions/10 days, dose per fraction = 3Gy, BED = 60Gy in 31 patients (72.09% of cases), TD = 20Gy/5fractions/5 days, dose per fraction = 4Gy, BED = 46.6Gy in 12 patients (24.91% cases).

At second radiation course, the fractionation schemas were TD = 15Gy/5 fraction/5 days, dose/fraction = 3Gy, BED = 30Gy in 13 patients (30.23% of cases), TD = 20Gy/10 fractions / 10 days, dose/fraction = 2Gy, BED = 33.2Gy in 29 patients (67.44% of cases). One patient only performed TD = 12Gy/3 fractions/3 days, due to his deteriorating performance status.

2.1. RADIOBIOLOGICAL CONSIDERATIONS

The effects of ionising radiation on the tissues vary in large range, from the radiation dose required to produce damage to the timing of damage expression. There are two categories of tissues: early-responding tissues (the effects of radiation damage occur within a period of days to weeks from the irradiation) and late-responding tissues (their response to radiation damage occurs months or years after the exposure). Some early-responding tissues are: skin, oral mucosa, intestines, bone marrow and testis. Examples of late-responding tissues: lung, kidney, spinal cord and central nervous system (CNS). Unlike early-responding tissues damages which can be reversible, the adverse effects on the late-responding tissues might be permanent and irreversible. The late reactions are the main limiting factor on treatment delivering [5].

The linear-quadratic model (LQ) has two components:

- **linear component** (\( \alpha D \)), directly proportional to delivered dose, \( D \), characterized by linear coefficient, \( \alpha \), corresponding to the cells that cannot repair themselves after one radiation hit and it is important for radiation with high linear energy transfer (LET);
- **quadratic component** (\( \beta D^2 \)) directly proportional to the square of dose characterized by the quadratic coefficient, corresponding to cells that stop dividing after more than one radiation hit, but can repair the
damage caused by the radiation and it is important for low-LET radiation [5, 6].

The linear coefficient, $\alpha$, indicates the intrinsic cell radiosensitivity, the quadratic coefficient, $\beta$, shows cell repair mechanisms, and it represents the natural logarithm of the proportion of repairable cells due to their ability to repair the radiation-induced effect of ionizing radiation [5, 6, 7].

The $\alpha/\beta$ ratio represents the dose for which the number of acutely responding cell deaths is equal to the number of late-responding cell deaths (the dose for which the linear and quadratic components of cell death are equal).

The CNS is less sensitive to radiation injury than some other late-responding tissues, such as lung or kidney. However, the damage to this organ results in severe effects, such as paralysis (after months or years), transitory demyelination (in the first 6 months), and leukoencephalopathy [8].

The most important radiation syndromes in the CNS develop in a few months to several years after therapy. The often-used separation into early or late delayed injury is not very useful, as different types of lesions with overlapping time-distributions occur. The radiation necrosis may also occur in 6 months, but even after 24–36 months [8].

From the histopathological point of view, changes that occur within the first year are frequently limited to the white matter. In the first 6–12 months post-irradiation, changes upon the grey matter occur; these changes manifest themselves in telangiectasia and focal haemorrhages. Brain radionecrosis have latent times between 1 and 2 years and it usually shows a mixture of histological characteristics [8].

3. RESULTS

Out of 43 re-irradiated M1BRA patients, 42 performed two courses of radiotherapy and only one received three courses of WBRT. The median time interval between the two courses of WBRT was 8 months [range 6–30 months]. The third radiotherapy course was also given 7 months after the second irradiation. The fractionation schema performed at third irradiation was: \( TD = 15\text{Gy}/5\text{fractions}, \) dose per fraction 3Gy, \( \text{BED} = 30\text{Gy}. \) At this patient we achieved a partial response and he lived 8 months after the last radiotherapy session.

The main goal of radiotherapy for brain metastases was the symptoms control. We evaluated the radiotherapy efficiency by neurological response. A complete/partial response was achieved in 30% and respectively 33% of cases. Stable disease/disease progression was recorded in 22% and respectively 15% of patients (Fig. 1). Median overall survival rate after re-irradiation was 3 months [range 1–18 months]. Only one patient survived 18 months (Fig. 2).
4. DISCUSSIONS AND CONCLUSIONS

Brain metastases signify the presence of progressive widespread disease which usually precludes a curative approach. Consequently, treatment has a palliative aim and M1BRA usually have a poor prognosis. Radiation therapy has proven efficacious in the palliation of brain metastases. Re-irradiation for recurrent
manifestations of brain metastases has been reported to be a benefit to either increasing the survival rate and/or improving the quality of life [8].

In case of re-irradiation, the normal tissues tolerance plays an important role in limiting dose [3]. A study of Thomas Diling et al. proposed dose constrains for brain being a BED value of 120 Gy (with TD = 72Gy, dose per fraction = 2Gy, \(\alpha/\beta = 3\) Gy) for 5% risk of radiation necrosis. The radiation necrosis is increased at 10% for BED =150Gy (with TD = 90Gy, dose per fraction = 2Gy, \(\alpha/\beta = 3\)Gy) [9].

A study of Sadikov et al. analyzed the value of whole brain re-irradiation in case of brain metastases. The radiation schemas used at the first radiotherapy course were TD = 20Gy/5 fractions, TD = 25Gy/10 fractions, TD = 30Gy/10 fractions. At the re-irradiation, fractionation schemas were between TD = 15Gy/5 fractions and TD = 25Gy/10 fractions. Patients with a documented response to re-irradiation had a median survival of 8.4 months, which was significantly longer than the median survival of non-responders 2.9 months [3]. The median survival after retreatment did not differ among three groups of patients with different time intervals between two brain irradiations. An analysis of the time between two radiation treatments and age as the continuous variable did not show any significant differences in survival [3].

There are several published reports describing many patients who were re-irradiated for symptomatic recurrent cranial metastases.

The largest retrospective study had 86 patients [10], used WBRT in a range of radiation doses (TD = 20Gy/10 fractions, TD = 30Gy/10 fractions) and reported varying proportions of improvement, from 27 to 75%. Kurup et al. analyzed 56 patients who performed re-irradiation for brain metastases in WBRT technique. Initial radiation therapy schedule was TD = 18Gy/6 fractions and re-irradiation schedule TD = 20Gy/10 fractions. The median time interval between two courses was median 7.8 months and the response was improved in 75% of patients [11].

There are few literature data regarding M1BRA re-irradiation and a single prospective study with 15 patients retreated with limited field radiation therapy, 30 Gy twice daily over 2 weeks; 60% of patients were reported as improved. Median survival rate is generally ranged between 1.8 and 4 months [3].

The rate of complications after WBRT depends on dose, fractionation, extent of disease, neurological impairment at presentation and age of the patient [12, 13].

Study of William A. Hall, et al. describes the clinical outcomes of the application of a novel technology to deliver repeat WBRT with volume modulated arc therapy (VMAT) and a simultaneous infield boost (WB-SIB) to gross disease. The median dose at reirradiation was 20Gy to the whole brain (median boost dose was 30Gy to gross disease). The median overall survival time after initiation of reirradiation for all patients was 2.7 months (range: 0.46 – 14.46 months). Side effects were manageable and comparable to other conventional repeat WBRT series. Repeat WB-SIB using the VMAT RT delivery technology is feasible and appears to have acceptable short-term acute toxicity [1].
There are 2 factors which influence the therapeutic decision of re-irradiation: the real benefit on improving neurological symptoms and neurological healthy tissue toxicity.

The treatment of patients who experience intracranial progression after whole brain radiation therapy (WBRT) is a clinical challenge.

Re-irradiation of M1BRA can represent an effective treatment for selected patients with good performance status and preserved neurological functions.

In our retrospective study we confirm some clinical benefit to re-irradiation in 19% of treated patients, and a median survival of 3 months in a group of patients who relapsed after an initial course of radiation therapy for brain metastases. Our current policy is to retreat selected patients with WBRT for multiple brain metastases based on performance status of patients.

REFERENCES