

Glioblastoma after radiotherapy for childhood acute lymphoblastic leukemia: Review

Çocukluk çağı akut lenfoblastik lösemi radyoterapisi sonrası gelişen gliyoblastoma: Derleme

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Abstract

Induction of neoplasia after therapeutic irradiation is well recognized. The development of the glioblastoma has been documented less frequently in association with radiation therapy. Pediatric patients with acute lymphoblastic leukemia are more susceptible to radiation-induced complications than adult patients. Post-radiation glioblastomas in childhood acute lymphoblastic leukemia have poor prognosis. Treating post-radiation glioblastomas are challenging for pediatric neuro-oncologists because of their more aggressive course than primary glioblastomas. To improve survival ratios and quality of life new researches are required in this treatment field. The goal of this review is to discuss the possible risk factors for radiation-induced tumorigenesis and histopathological characteristics.

Keywords: Chemotherapy, glioblastoma, leukemia, radiation

Özet

Radyasyon tedavisinin tümör gelişimine neden olduğu iyi bilinmektedir. Radyasyon tedavisi ilişkili gliyoblastom oluşumu çok az rapor edilmiştir. Akut lenfoblastik lösemili çocuk hastalar radyasyonun neden olduğu komplikasyonlara karşı yetişkinlerden daha duyarlıdır. Akut lenfoblastik lösemili çocuk hastalarda radyasyon tedavisi sonrası gelişen gliyoblastom olguları primer gliyoblastomaya göre kötü seyirlidir ve çok agresif davranışlı olduğundan dolayı nöro-onkologlar için tedavisi zordur. Bu hasta grubunun tedavisinde hayat kalitesini ve sağ kalımı artırmak için yeni araştırmalar gerekir. Bu derlemenin amacı gliyoblastomanın histopatolojik karakteristik özelliklerini ve radyasyonun tümörojeneze neden olan risk faktörlerini literatür eşliğinde tartışmaktır.

Anahtar kelimeler: Kemoterapi, gliyoblastom, lösemi, radyasyon

Introduction

Radiation therapy (RT) is an important modality for acute lymphoblastic leukemia (ALL) patients with high risk factors and/or central nervous system (CNS) involvement at the time of diagnosis, or for ALL patients with CNS relapse (1). RT, in compatible with chemotherapeutic agents, has been well documented in the prophylaxis of high risk ALL in pediatric patients in order to provide long-term disease free survival times. Radiation-induced tumor development is more commonly observed as more prolonged survival times obtained due to improvements in treatment modalities.

The development of glioblastoma multiforme (GBM) in ALL patients after prophylactic cranial irradiation (PCI) and chemotherapy (CHT) has been reported less frequently. In the present study, we primarily focused on the patients who developed GBM after receiving PCI for childhood ALL, and also focused on the possible risk factors for radiation-induced tumorigenesis and histopathological characteristics.

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We discussed these issues through a comprehensive review of the literature.

Methods

We reviewed all cases of intracranial GBMs with a positive history of previous PCI. This was performed by searching the key terms of "GBM, RT, and ALL" in PubMed, Ovid and Google Scholar databases.

Literature review

Through a comprehensive review of the literature we identified 30 cases -including our 2 cases- in which GBM developed after PCI (Table1) (2-16). Radiation-induced GBM in ALL patients was first reported by Chung et al. in 1981 (2). According to that report, a 2-year-old child with ALL received systemic CHT and CNS irradiation with intrathecal (ith) methotrexate (MTX) for CNS prophylaxis. While ALL was in remission, GBM with a large cyst developed at left parietal area after 5 years. The patient underwent surgery and received adjuvant RT (50 Gy). The patient survived only 10 months from the onset of the GBM diagnosis.



Table 1. Cases of GBM after prophylactic treatment of ALL

| Authors | Sex | Age | Radiation Dose (Gy) | Latency (months) | Survival (months) |
|----------|-----|------|---------------------|------------------|-------------------|
| Bien | F | 9.5 | 12 | 54 | 19 |
| Bien | M | 6.8 | 12 | 58 | 5 |
| Borgman | F | 7.7 | 18 | 65 | 14 |
| Chung | M | 2 | 24 | 63 | 10 |
| Donson | F | 14 | † | 120 | 3 |
| Fontana | M | 6 | 24 | 120 | 6 |
| Fontana | M | 3 | 24 | 110 | 14 |
| Joh | F | 17 | 19.5 | 72 | 11 |
| Menon | F | 4 | 18 | 11 | 15 |
| Menon | M | 6 | 18 | 36 | 8* |
| Menon | M | 10 | 18 | 72 | 6* |
| Muzumdar | M | 12 | 20 | 72 | 2* |
| Present | F | 3.5 | 15 | 5 | 2 |
| Present | M | 4 | 12.6 | 75 | 14* |
| Relling | † | 2.7 | † | 60 | † |
| Relling | † | 10.3 | † | 84 | † |
| Relling | † | 15.9 | † | 72 | † |
| Salvati | M | 12 | 24 | 72 | 5 |
| Salvati | F | 10 | 24 | 132 | 14 |
| Salvati | F | 10 | 24 | 144 | 1 |
| Salvati | M | 25 | 24 | 132 | 7.6 |
| Sanders | F | 4 | 24 | 60 | † |
| Shah | M | 11 | 18 | 60 | † |
| Shapiro | F | 6 | 24 | 48 | † |
| Symss | M | 4 | 12 | 34 | † |
| Walter | M | 2 | 18 | 132 | 0.1 |
| Walter | M | 2.7 | 24 | 90 | 25 |
| Walter | F | 5 | 48 | 69 | 7 |
| Walter | M | 15 | 24 | 108 | 18 |
| Yaris | M | 13 | 18 | 60 | 6 |

* Alive when the paper was written

† Not specified within the article

ALL, acute lymphoblastic leukemia;

GBM, glioblastoma multiforme

Although no significant association exists between sex and development of secondary brain tumors (10), the incidence of SMNs are 1.5 times higher in males. Median age was 7.3 (2-25). The mean latency time for the development of radiation-induced GBM was 76.3 months (5-144). This is a shorter duration as compared with other radiation-induced tumors (109-132 months) (15,17); however, in radiation-induced glial tumors the duration was similar relative. In addition, latency periods were 64.8 months for patients less than 7 years old and 89.6 months for those above 7 years old. The survival time after GBM was 38 weeks (1-100) in the present study. This duration is shorter than de novo GBMs (119 weeks) (18). The mean radiation dose was 2058 cGy (1200-4800).

Discussion

Pediatric patients are more susceptible to radiation-induced complications than adult patients and have higher incidence of complications and develop neurotoxicity earlier (19). Prior exposure to ionizing radiation is known to be a risk factor for the development of primary CNS tumors. Development of post-irradiation tumors in the CNS was first reported by Mann et al. (20), and the role of radiation on tumorigenesis of the brain was first documented by Modan et al (21). Subsequently, several cases of radiation-induced CNS tumors including GBM,

anaplastic astrocytoma, sarcoma, meningioma, and schwannoma have been reported.

In long-term survivors among children who were given PCI for ALL, the incidence of primary brain tumors is 2.3%, which is a 22-fold increase relative to the expected incidence of non-cranially-irradiated patients (22,23). Although the role of PCI in the treatment of pediatric ALL has been decreasing in the recent years, RT remains to be important in the management of high risk ALL patients. RT is most commonly performed focally; hence, secondary tumors most commonly develop within or near the RT field. Cahan et al. (24) presented a criteria for radiation-induced tumor which was modified subsequently include the following: 1) secondary tumor must originate in the previous RT field, 2) histologically proven difference must be between primary and secondary tumor, 3) a sufficiently long time period must be between RT and the onset of a secondary tumor (usually > 5 years), and 4) patient must not have a mutator phenotype which favors the development of this kind of tumors such as Li-Fraumeni syndrome and retinoblastoma.

Risk factors of radiation-induced GBM

Development of a secondary malignancy is one of the most devastating events in childhood ALL. Cranial or craniospinal irradiation is an important risk factor for the development of secondary CNS malignancies. However, the exact mechanism playing a role in radiation-induced tumorigenesis in humans and experimental animal models has not been well understood. Several factors were blamed for the development of radiation-induced brain tumors

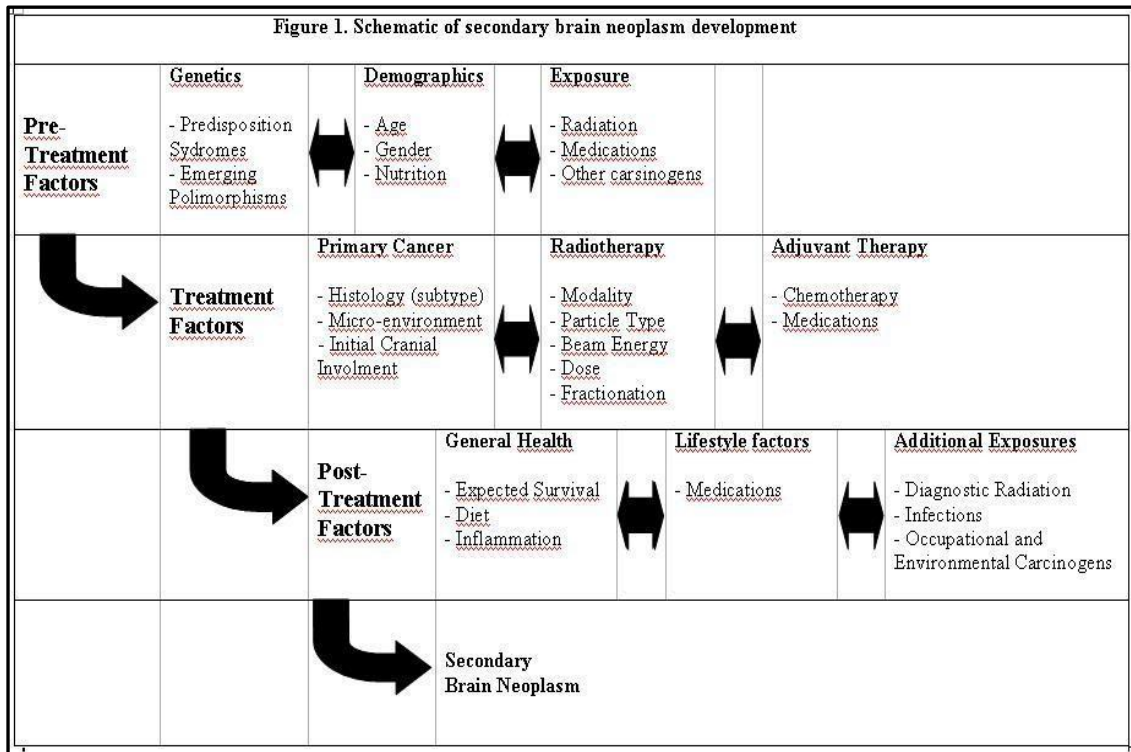


Figure 1. Schematic of radiation-induced secondary brain neoplasm development

including irradiation dose, young age at time of RT, timing of antimetabolite CHT, initial CNS infiltration, and genetic makeup (Figure 1).

1. CNS radiation therapy

The tumorigenic effects of radiation on normal tissues are explained by genetic alterations and genomic damage. Beside these mutagenizing effects, post-radiational micro environmental changes are remarkable. Radiation-induced tumors most commonly raised in the irradiated regions or within the irradiation-fields. Transmission of radiation-induced signals between irradiated cells and adjacent non-irradiated cells might cause generation of reactive oxygen/nitrogen species in the non-irradiated cells, which might promote tumorigenesis. This is called as “by stander effect” and the mechanisms underlying bystander effect are not well defined, however some cytokines and/or intercellular gap junctions are considered responsible (25-27).

It has been reported that the incidence of GBM among survivors of post-PCI childhood ALL was 1.3% (10). In the large retrospective cohort study of Neglia et al. (23), children with ALL received previously a dose of 18-24 Gy PCI or craniospinal irradiation developed CNS neoplasms. They demonstrated a 7-fold increase of all cancers and a 22-fold increase of CNS neoplasms. Relling et al. found that the incidence of brain tumors among in ALL children who received PCI was higher than in children who did not receive

(9). Nygaard et al. (28) reported that the estimated cumulative risk of developing secondary malignant neoplasms within 20 years was 2.9%. The corresponding risk for PCI-given ALL children was 8.1% compared to 0.3% for those who did not receive PCI.

2. Irradiation doses

The standard prophylactic dose of cranial irradiation was defined as 12 Gy in the BFM trials in the mid-1980s. The dose of the cranial irradiation (12 Gy vs 18 Gy and more) and the incidence of secondary malignant neoplasm (SMN) were related (29). Borgman et al (4) demonstrated that the rate and cumulative incidence of SMN were significantly higher in patients receiving cumulative PCI doses >18 Gy. In another study, most SMNs were shown to develop after higher doses of radiation (more than 30 Gy) (9,15). However, patients who had leukemic infiltration of the CNS at the initial diagnosis of ALL required higher doses of PCI. On the other hand, increased incidence of SMNs in these patients is likely related to higher doses. In addition, as compared with a dose of 2400 cGy cranial irradiation, with a dose of 1800 cGy reduced risk of neurological (i.e. neurocognitive and neuroendocrine) toxicity was reported (9,30).

3. Chemotherapy

A clear relationship between some chemotherapeutic agents and secondary myeloid leukemia determined, however, the available data is not enough to establish

an association between systemic CHT and brain tumor occurrence. Stand-alone ith CHT (i.e. MTX) or In combination with RT constitutes a significant part of ALL therapy and is highly effective for prevention of first CNS relapse. Relling et al. (9) reported a higher incidence of secondary brain tumor in ALL patients treated with higher doses of 6-mercaptopurine which was related to a genetic defect in the thiopurine metabolism. On the other hand, any variability in antimetabolite metabolism was not defined a risk factor and the use of ith CHT was not found to increase the risk secondary brain tumor development (15). Rosso et al. (31) demonstrated a synergistic effect of RT and ith MTX which were administered before PCI. In addition, IV high-dose MTX was shown to be responsible for the development of leukoencephalopathy in children with ALL (32). However, that MTX alone may contribute to tumorigenesis or not and that it increases the carcinogenic effect of irradiation are debated.

4. Young age

In several multi-center studies, a clear relationship between young age at ALL diagnosis and the increased risk of SMN development were determined, with the risk considerably increased below age 7 (15,29). The cumulative SMNs probability after 15-years were 1.5% above/years and 0.1% below 7 years (29). Moreover, we found GBM developed earlier in patients <7 years than in >7 years (64.8 months vs 89.6 months). Major mechanism for the observed tendency to develop SMNs in children relative to adults might be due to genotoxic injury to stem cells which are generally more active in children. In addition, this difference might be related to better survival times in children (33).

5. Genetic background

Risk factors for radiation-induced brain tumors are background harboring germline mutations in tumor suppressor genes (34). In general, individuals with tumor predisposition syndromes (such as Cowden's disease, tuberous sclerosis, Neurofibromatosis I and Li-Fraumeni syndrome) should be considered at risk for SMNs after RT. SMN development also may be affected by polymorphisms (such as genetic polymorphisms of thiopurine S-methyltransferase) in metabolic pathways which result in alterations in the repairment of radiation-induced genotoxic damage (35).

In addition, radiation-induced damage may lead to mutation and chromosomal aberration, leading to neoplastic transformation. In pediatric gliomas, chromosomes 3, 7, 9 and 17 are most frequently involved in structural abnormalities (36). The bcr-abl fusion with Philadelphia chromosome (9: 22 translocation) is believed as a poor prognostic factor. In the recent years, Yaris et al. (16) reported a secondary GBM in a patient with a new translocation

t(3; 3) (q21; q26) after ALL treatment. Chromosomal aberrations may vary case by case and are required to be determined in order to define the underlying mechanism of the development of secondary GBM (7).

Histopathological characteristics of GBM

Differences between radiation-induced gliomas and "de novo" ones have not been identified by radiographic, histopathological and genetic alterations. Donson et al. (5) demonstrated greater homogeneities of gene expressions in radiation-induced GBMs than "de novo" GBMs by their methods of molecular analyses. In contrast, Brat et al. (37) could not demonstrate molecular differences between two groups. Salvati et al. (10) found no peculiarities in methyl-guanine-methyl-transferase enzyme gene promoter methylation status and YKL-40 staining level. In these studies, surgical specimens from GBM patients were analysed using gene expression microarray. Radiation-induced GBMs were found more aggressive and treatment-refractive than "de novo" ones, which shows heterogeneous pattern of gene amplification as compared to homogeneity pattern of radiation-induced GBMs. These may suggest radiation-induced GBMs have common and shared tumorigenic origins and pathways (10).

In conclusion, RT continues to be an important component of children with high-risk ALL. As cancer survival improves, late effects of RT can negatively impact long-term patient health. The most significant and life-threatening late effect is the development of a radiation-induced tumor such as GBM. Fortunately, GBM development in ALL after PCI is infrequent. RT and CHT is a well-known predisposing factor, however, genetic susceptibility to GBM development might contribute simultaneously. Most radiation-induced GBMs in childhood ALL have poor prognosis and are challenging for pediatric neuro-oncologists to treat due to their aggressive course. In the treatment radiation-induced GBMs CHT regimes are not very effective and RT may not be an option due to prior irradiation. To improve survival and quality of life new studies are required.

Acknowledgements

We thank all the staff of the Department of Radiation Oncology for their contributions.

Conflict of Interests

The author declares no conflict of interests.

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How to cite:

Kuzhan A. Glioblastoma after radiotherapy for childhood acute lymphoblastic leukemia: Review. Gaziantep Med J Gaziantep Med J 2015;21(2):125-130.