Review Article

Examining the Survival benefit of Radiation Therapy on Leptomeningeal Carcinomatosis and Identifying factors Associated with Survival Benefit of WBRT

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Abstract

Purpose: To report the survival benefit of Radiation Therapy (RT) in Leptomeningeal Carcinomatosis (LMC) patients with different primary cancers and to identify the factors of LMC patients that had survival benefit from Whole Brain Radiation Therapy (WBRT).

Methods and Materials: Systematic literature review was performed. Search terms included 'Leptomeningeal', 'prognostic factors' and 'lung' or 'breast'. Literatures were included if patient profile was reported. Specifically, age, median survival, diagnosis time line, type of cancer, received treatments, performance score, and systemic disease were sought after. Literatures were excluded if they were a) case reports, b) written in language other than English, or c) not including patient profile.

Results: RT treatment has survival benefit for LMC patients with CSF obstruction. For LMC patients with primary breast cancer, 7 studies were found since 1991 that met searching criteria. Factors which would allow breast cancer-caused LMC patients to benefit from WBRT with survival are identified with statistical significance. They include KPS>60, Intrathecal (IT) chemotherapy, systemic therapy, hormonal receptor status and severity of systemic disease. Patients who met aforementioned criteria and received WBRT had longer median survival (17 weeks vs. 11.9weeks, p=0.015). Similarly, 10 studies were found that met searching criteria for Non-Small Cell Lung Cancer (NSCLC) caused LMC. Beneficial factors for NSCLC-caused LMC are identified. They include IT chemotherapy, KPS > 60, and EGFR TKI treatment. Patient who met these criteria had longer median survival when received WBRT (17.6 weeks vs 12.2 weeks, p = 0.0412).

Conclusion: Profiles of LMC patients that can benefit with longer survival by receiving WBRT are identified for breast cancer and NSCLC. Algorithms in identifying such patients are provided.

Short Description of this Paper

Today, there is not conclusive data on the survival benefit from radiation therapy for leptomeningeal carcinomatosis patients. Based on published data, the survival benefit of the radiation therapy is reviewed. For breast and NSCLC primary cancers, profiles of LMC patients that experienced survival benefit from Whole Brain Radiation Therapy (WBRT) are identified.

Introduction

Prevalence of Leptomeningeal Carcinomatosis (LMC) is reported to be about 5% of all the patients with cancer [1]. LMC is a detrimental complication of cancer involving the CNS. Without treatment, the median survival from the diagnosis is 4-6 weeks, and with treatment, it is doubled to 8-12 weeks [2-5]. The incidence of LMC has been increasing for the past several decades. Such increase is partially due to a) improved diagnostic modalities, including fine resolution MRI and CT, and b) improved cancer treatment [6]. Paradoxically, with cancer treatment improvement, the risk of LMC increases as the chance for cancer cells to invade the subarachnoid space is increased over time. Today, there is no clear standard of care to treat LMC patients. Due to relatively short median survival, a careful weighing between prolonging lifewhile worsening the quality of life and maintaining the pain-free quality of life without prolonging life needs to be evaluated and discussed with the patient.

As of today, intra-thecal (IT) chemotherapy is the mainstay of the LMC treatment [7,8]. The most common method is using the ommaya reservoir and directly injecting chemotherapeutic agents into the CSF. Many have reported that IT has survival benefit for good risk patient group [9-11]. Radiation Therapy (RT), often used in conjunction with the IT, is used to target symptomatic sites and to relieve mass effect [12]. However, the effectiveness of radiation therapy on overall survival has not been as conclusive as IT treatment. This is partially due to poor prognosis with a short median survival. Such combination along with rapid deterioration of neurologic functions makes randomized trials very challenging. Therefore, RT is mainly considered to be supplemental
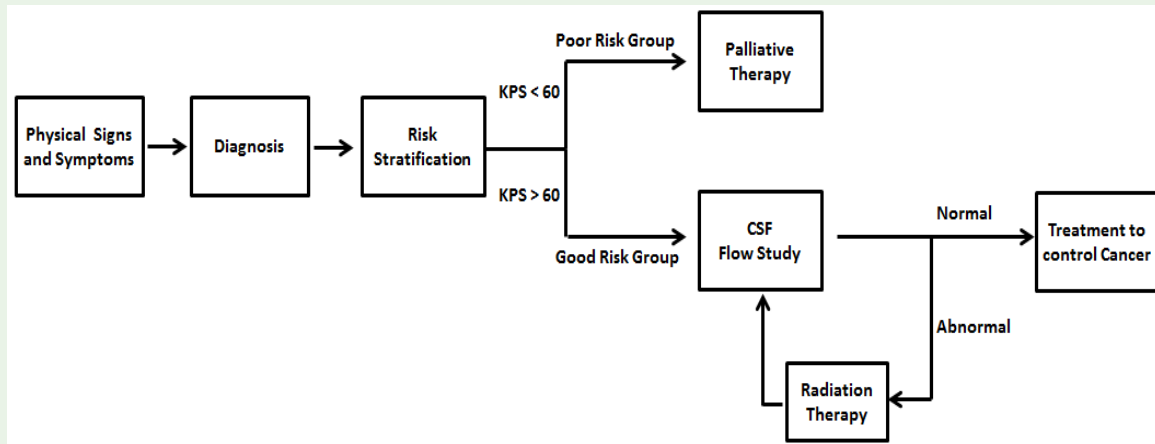
Figure 1(a): Simplified Algorithm of the LMC treatment.

therapy to IT. For the past decades, multiple retrospective studies were published with conflicting conclusions on the survival benefit of RT. This is mainly because multiple factors contribute to not only clinical progression but also survival. Therefore, it is important to keep such complex dynamics into account when treating/assessing LMC patients.

The purpose of this review is two-fold. The first purpose is to examine the effectiveness of radiation therapy in prolonging the survival of LMC patients. Second is for different primary cancers; identify constituting factors that would allow LMC patients to have survival benefit when treated with RT. Differentiating factors for breast cancer and lung cancer is crucial as treatment planning including RT changes. Based on identified factors, general algorithm for breast cancer and lung cancer will be devised.

Treatment Overview

LMC management overview

Figure 1 shows the simplified treatment algorithm for LMC patients. Such algorithm was derived from NCCN guideline [13] shown in detail in Figure 2. Once the diagnosis of LMC is made, the patient is further stratified into either poor-risk or good-risk groups, as shown. For poor risk groups, the therapy is mainly supportive with palliative therapy. On the other hand, for the good-risk group patients, the goal is to control the cancers by aggressively treating the patients. Treatment goals include improving or stabilizing the neurologic function, improving the quality of life, or prolonging life [14]. Achieving any of the three listed treatment goals would consider such treatment effective. For patients that are receiving WBRT, it is recommended to cover the meningeal space, including the lamina cribrosa and basilar cistern.

CSF flow study, radiation therapy and survival benefit

Before the intra-CSF chemotherapy is started, a CSF flow study is recommended, as shown in Figure 1. As cancerous cells invade
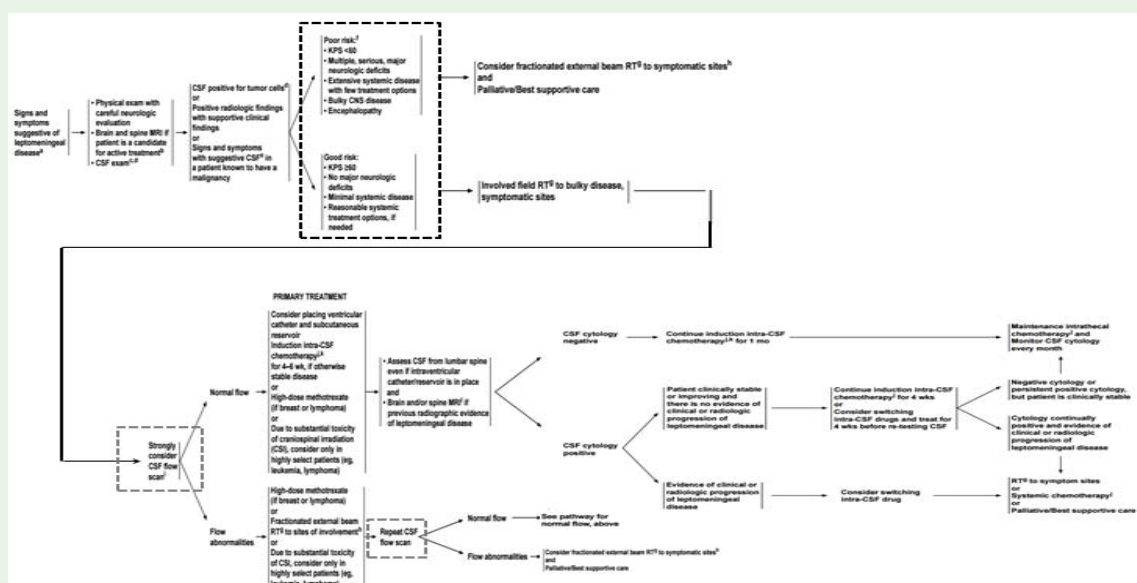
Figure 1(b): Complete Algorithm of the LMC treatment from NCCN.

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Figure 2: CSF Flow Abnormality Correction with RT and Survival Benefit.
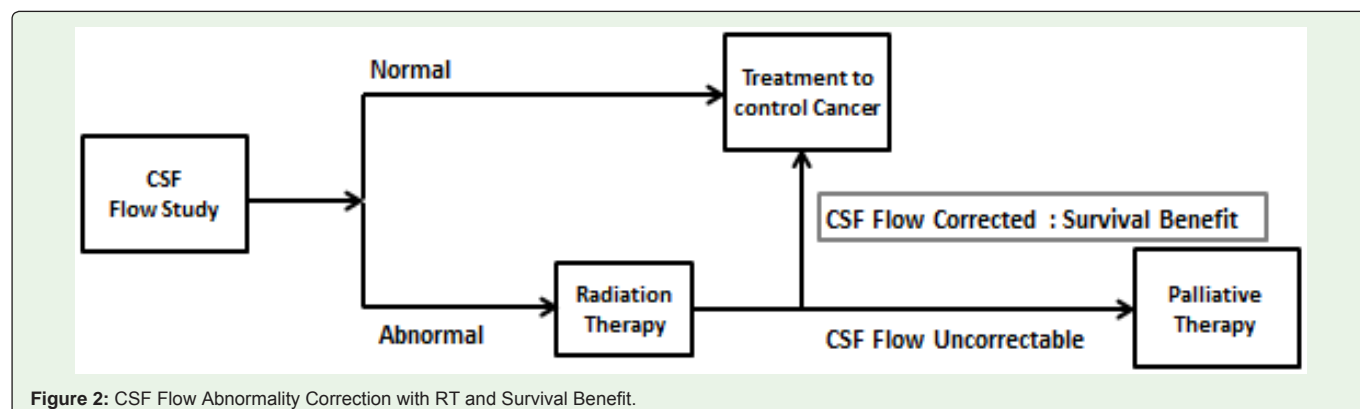
the subarachnoid space, they can block the CSF outflow. More than 50% of LMC patients are reported to have CSF Flow Abnormality and as high as 70% has been reported by Grossman et al., [15]. As outflow is disturbed, hydrocephalus develops and Intracranial Pressure (ICP) can be elevated. This explains why more than 50% of LMC patients report headache as their chief complain [16]. More importantly, without normal CSF flow, intra-CSF chemotherapy is not recommended due to the possibility of developing neurotoxicity. Intra-CSF chemotherapy relies on normal CSF flow to be distributed throughout the entire neuraxis. CSF flow obstruction will cause toxic chemo agents to build up within the subarachnoid space, a phenomenon described as 'protected site effect' by Glantz et al., [17], and cause more toxicity than benefit.It has been reported that such toxicity affected the survival of the LMC patients [18]. In order to assess CSF flow, either Technetium or Indium-DPTA is used [19]. Once the dye is injected, images are taken in such an order that certain compartments should be clear of dye with the elapse of time. Typically, dyes reach the basilar cisterna, lumbosacral sac, and leave the entire ventricle within 10 minutes, 2 hours, and 24 hours, respectively [15,17,20].

Sensitivity, selectivity and accuracy of CSF flow study is over 99%, whereas detecting flow abnormality using MRI or CT are 60% and 30%, respectively [21]. Once the flow abnormality is detected, focal radiation therapy is used to correct the obstruction [22]. The localized spot is mapped to the brain scan images and radiation is used to treat the obstruction. Glantz et al., [17] and Chamberlain et al., [23] reported survival benefit of RT in LMC patients with flow abnormality. Table 1 summarizes the finding of Glantz et al., [17]. Similar findings have been reported in Grossman et al., [15], and Chamberlain et al., [24].

Radiation therapy hence indirectly provides survival benefit by resolving the obstruction and by allowing effective IT treatment to take place. CSF flow study has been incorporated as part of the LMC treatment guideline. Based on aforementioned findings, the diagnostic and survival algorithm for CSF outflow abnormality can be

designed as shown in Figure 2. If the obstruction is corrected, which is shown in the red box from the Figure 2, survival benefit can result.

Breast cancer caused LMC

Breast cancer is the most common solid tumor causing LMC, as it comprises 35% of total solid tumor-based LMC patients [4,6,25]. The breast-cancer-caused LMC rate has been increasing for the last decade mainly due to improvement in breast cancer treatments [1,26]. For breast cancer, the tumor cells directly invading the subarachnoid space is thought to be themost likely causeof dissemination to the meninges [27,28]. The median survival of patients with breast cancer is the highest compared to other primary cancers with 9-30 weeks [10,29,30]. Most common histologic types and biologic subtypes for breast cancer LMC are lobular and triple-negative, respectively [31-33]. This is contrary to the fact that the most common biologic subtype in the general breast cancer population is luminal A [31]. A summary of breast cancer causedLMC is summarized in Tables 1&2.

For patients with normal CSF outflow, IT therapy has shown survival benefit for breast cancer caused LMC patients [10,17,29,30,34]. On the other hand, the survival benefit of radiation therapy on breast cancer LMC patients has not been clearly established. In order to study the radiation therapy's benefit on the overall survival of LMC patients with primary breast cancer, seven papers meeting the searching criteria were found dating from 1991 to 2013. All seven papers discussed radiation therapy as a treatment modality and discussed prognostic factors for LMC patients with breast cancer. Table 3 summarizes the 7 studies and the patient demographics for each study.

As can be seen from Table 3, only two studies Rudnick et al., [35] and Niwinski et al., [31] showed survival benefit with the WBRT. These two studieswere compared tothe other five studies. Table 4 shows the comparison of patients who experienced survival benefit with WBRT. Statistically significant factors include KPS score, IT chemotherapy, systemic Therapy, hormonal receptor status and

Table 1: Survival Benefit after CSF Flow correction with RT [17].

Flow Status	Survival
Normal (N=13)	6.9 month
Abnormal but corrected with RT(N=9)	13 months
Abnormal but uncorrectable (N=9)	0.7 month

Table 2: Summarizing the breast cancer type LMC.

Prevalence (among solid tumor LMC)	35%
Median Survival	9-30 weeks
Most common histologic sub-type	Lobular
Most common biologic sub-type	Triple-Negative
Most common treatment for OS	IT chemotherapy

Table 3: Summary of breast cancer patients with LMC published in last 20 years.

	Boogerd (1991)	Jayson (1994)	Fizazi (1996)	Rudnick (2007)	Gauthier (2010)	De Azevedo (2011)	Niwanski (2013)
Number of Patient	44	35	68	67	91	60	118
Median Age	57	45	52	49	53	46	49
Median Survival	12	11	9.5	16	14	13	18
Time from BR to LMC(months)	38	20	30	27	22	17.9	25
KPS Score> 60	N/A	N/A	34	41	N/A	47	80
KPS Score < 60	N/A	N/A	34	26	N/A	12	38
Intra-CSF Chemo	44	1	41	57	80	41	93
Systemic	20	N/A	42	41	72	13	80
WBRT	22	8	18	33	26	22	66
WBRT benefit on OS	no	No	no	yes	No	No	Yes
Ductal Carcinoma	N/A	N/A	29	23	52	47	54
Lobular	N/A	N/A	29	22	23	13	32
ER/PR Positive	17	N/A	13	37	60	28	49
Systemic Metastasis	28	N/A	47	29	67	47	57
Most Common	Bone	N/A	bone	Bone	bone	Bone	Bone

severity of systemic disease. Patients that benefited from WBRT had longer median survival with 17 weeks compared to 11.9 weeks with statistical significance (p = 0.015). Patients in the benefited group used more multi-modality treatments, including intra-CSF, systemic, and WBRT (53% vs 33%). Also, the systemic metastatic involvement was substantially lower in the benefitted group (46% vs 67%). Based on Table 4, an algorithm can be created for those who can potentially benefit with longer survival from the radiation therapy (gray box), as shown by Figure 3.

Lung cancer caused LMC

Lung cancer is the second most common cause of LMC from solid tumors, comprising about 20% [36]. Without treatment, survival is 4-6 weeks. With treatment, survival can be extended to 16 to 24 weeks [20]. Non-Small Cell Lung Cancer (NSCLC) is the most common cause, constituting >80 % of LMC patients [37]. For NSCLC-caused LMC, retrograde flow to the vertebral and para-vertebral venous system with an increased intra-thoracic pressure is believed to be the most common cause of gaining access to the subarachnoid space [27,28]. The most common histologic type is adenocarcinoma, making up more than 85% of lung cancer caused LMC. Current treatment modalities for NSCLC caused LMC includes IT chemotherapy, systemic therapy, RT, and Epidermal growth factor tyrosine kinase inhibitor (EGFR-TKI). Like breast cancer caused LMC, there is no standard treatment protocol as of today. Summary of lung cancer caused LMC is summarized in Table 5.

IT chemotherapy has consistently shown survival benefit for NSCLC caused LMC patients [38-41]. For the past decade, adding EGFR-TKI targeted therapy to the treatment has shown substantial improvement in survival consistently. Nakamura et al., [42] showed patients with EGFR-TKI regiment had median survival of 13 months

Table 4: Analysis of factors associated with survival benefit of WBRT.

	WBRT with Survival Benefit (2 Studies)	WBRT without Survival Benefit (5 Studies)	P Value
Number of Patients	185	207	
Median Age	49	50.6	0.68
Median Survival(weeks)	17	11.9	0.015
Time from BR to LMC(months)	26	25.5	0.94
KPS Score > 60	121 (65%)	109 (52%)	0.01
KPS Score < 60	64 (34%)	97 (46%)	0.0137
Intra-CSF Chemo	150 (81%)	127 (61%)	<0.0001
Systemic	121 (65%)	90 (43%)	<0.0001
WBRT	99 (53%)	70 (33%)	<0.0001
Ductal Carcinoma	77 (41%)	76 (36%)	0.55
Lobular	54 (29%)	42 (20%)	0.49
ER/PR Positive	86 (46%)	41 (19%)	0.01
Systemic Metastasis	86 (46%)	140 (67%)	<0.0001
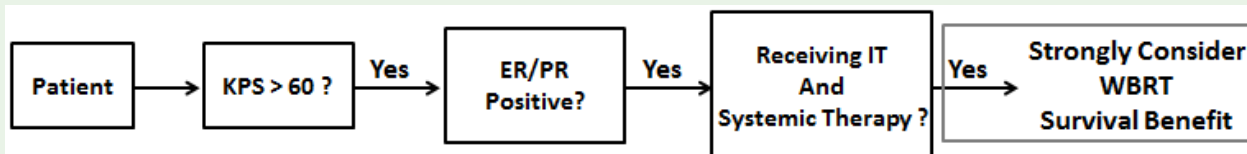
Figure 3: Algorithm for recommending RT therapy for survival benefit based on 7 studies.

Table 5: Summarizing the LMC with primary lung cancer.

Prevalence (among solid tumor LMC)	20%
Median Survival	12-18 weeks
Most common histologic sub-type	NSCLC
Most common cytology	Adenocarcinoma
Most common treatment for OS	Intra-Thecal

compared to 4 months of those without EGFR-TKI treatment [42]. Similar results were reported from Morris et al., [39], Lee et al., [40], and Xu et al., [43]. On the other hand, the survival benefit from RT has been reported with inconsistent conclusions. In order to make a more concrete conclusion on the survival benefit of the RT of LMC patients with primary lung cancer, ten papers from 1998 to 2015 were reviewed. All ten papers included WBRT as a treatment modality and discussed prognostic factors for LMC patients with NSCLC. Table 6 summarizes the results.
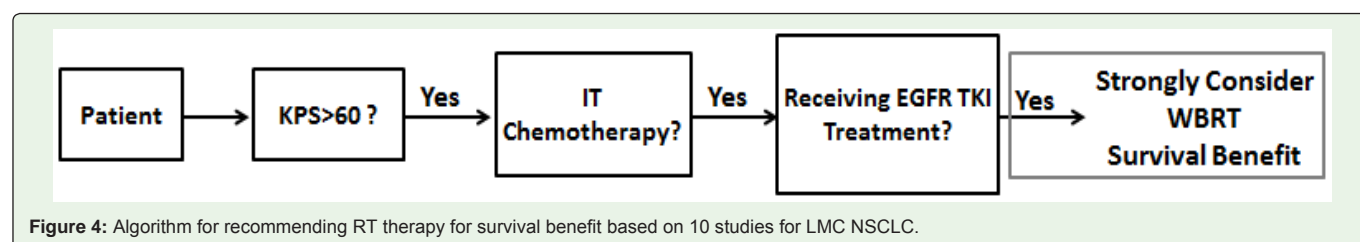
Table 6: Summary of NSCLC patients with LMC published in last 20 years.

	Chamberlain (1998)	Chuang (2008)	Park (2010)	Nakamura (2012)	Morris (2012)	S Lee (2013)	Xu (2015)	Umemura (2012)	Gwak (2011)	Riess (2014)
Number of Patients	32	34	50	67	125	149	108	91	105	30
Median Age	57	60	62.5	64	59	58	61	62	56	58
Median Survival (weeks)	20	5.1	22	17	12	14	21	14	12	12
Lung to Diagnosis (month)	7	7.1	10.2	12	15	11.1	12	12.2	17	16.4
Adenocarcinoma	24	32	42	67	97	135	85	83	101	30
Intra-CSF	32	2	48	37	7	109	42	27	59	2
systemic	20	20	22	37	20	29	59	51	53	21
WBRT	9	10	27	29	46	67	49	21	18	19
WBRT Survival	No	No	yes	yes	no	yes	yes	yes	No	no
ECOG PS <=2	32	17	35	37	63	129	87	52	50	14
ECOG > 2		17	15	30	62	20	21	39	55	16
EGFR TKI	0	0	14	37	9	24	42	51	29	21

Table 7: Analysis of factors associated with survival benefit of WBRT.

	WBRT with Survival Benefit	WBRT With No Survival Benefit	P value
	(5 studies)	(5 studies)	
Number of Patients	465	326	
Median Age	61.5	60.4	
Median Survival (weeks)	17.6	12.2	0.0412
Lung to Diagnosis (month)	14.24	12.5	0.56
Adenocarcinoma	412 (87%)	284 (87%)	0.94
Intra-CSF	226 (49%)	102 (31%)	<0.0001
Systemic	198 (43%)	134 (41%)	0.29
WBRT	193 (41%)	102 (31%)	0.0063
ECOG PS <=2	340 (73%)	176 (54%)	<0.0001
ECOG > 2	125 (26%)	150 (46%)	<0.0001
EGFR TKI	168 (36%)	59 (18%)	<0.0001

Figure 4: Algorithm for recommending RT therapy for survival benefit based on 10 studies for LMC NSCLC.

Five out of ten studies reported survival benefit with WBRT. Table 7 shows the comparison of LMC patients who experienced survival benefit with WBRT.

Statistically significant factors include IT chemotherapy, performance score, and EGFR TKI treatment. The median survival was higher among patients who benefited longer survival with WBRT (17.6 weeks vs 12.2 weeks). The performance score was substantially better for those who benefitted the longer survival with WBRT. Not surprisingly, the group with benefitted survival from WBRT had substantially higher percentage treated with EGFR-TKI (36% vs 18%). Based on such findings, a general algorithm for a patient with LMC with NSCLC who can potentially experience survival benefit from WBRT (gray box) can be created, as shown by Figure 4.

Discussion

To our knowledge, this is the first synthesized literature review analyzing factors that have statistical significance in regards to survival benefit of RT in LMC patients. Many retrospective studies have been published with different conclusions on relationship between RT and its survival benefit. Such conflicting results are not surprising given the nature of retrospective study, complex treatment regimen of LMC patients, and varying degree of prognostic factors associated with patient population in different studies. Therefore, systemic review on published studies to investigate the inconsistent conclusions on survival benefit of RT and identifying factors that lead to the discrepancy would benefit clinicians in providing optimal treatment to LMC patients.

The role of RT for LMC patients comes in two-folds. First role is to facilitate successful treatment course of IT chemotherapy by correcting CSF outflow obstruction which exists in more than 50% of LMC patients [15]. Second role is to relieve symptoms and mass effects. RT has shown survival benefit in both categories [17,31,40].

Indirect survival benefit of RT by correcting CSF outflow obstruction is reported by multiple studies [15,17,44]. In study by Glantz et al., [17], patients who started with abnormal CSF flow and corrected with RT (n =9) had longer median survival than those with normal CSF flow (n=13) with statistical significance (13 months vs 7 months). In addition to correcting obstruction, performance and extent of systemic disease involvement were reported to have contributed to longer survival compared to normal-flow patients. But in the same study, patients with CSF outflow abnormality that were not correctable with RT (n=9) had much shorter median survival compared to those corrected (13 months vs 0.7 months). Among uncorrectable population, only 2 out of 9 patients had significant performance degradation with cranial nerve involvement compared to outflow-corrected group. Otherwise, performance characteristics and systemic involvement were very similar between two groups.

Hence, there is a clear survival benefit if CSF out flow obstruction can be corrected. Therefore, it is important to emphasize how RT plays a vital role allowing IT chemotherapy to work properly which is the mainstay of LMC treatment today. Today, NCCN guideline strongly recommends CSF flow study once LMC patient is categorized into good risk group.

For LMC patients from the breast cancer, seven studies were identified that met our searching criteria. Two of seven studies concluded WBRT has survival benefit. Using survival benefit with WBRT as a variable, two groups were created. Group1 (n=185) was from two studies [31,35] that showed survival benefit and group2 (n = 207) from studies that did not show survival benefit with the WBRT. Group1 had longer median survival compared to group 2 (17.6 vs. 12.2 weeks) with statistical significance. Factors that showed statistical significance between group1 and group 2 included KPS>60, IT chemotherapy, systemic treatment, WBRT, and the severity of systemic disease including metastases to other organs.

In general, KPS score is a strong prognostic factor for all cancer treatments [45]. All seven studies reported KPS>60 to be a positive prognostic factor for overall survival regardless of the survival benefit from theWBRT. KPS score is directly related to the status of the CNS involvement and recent study showed that there is a correlation between high KPS score and survival benefit from WBRT for patients with CNS metastasis [46,47].Therefore, higher performing patients benefit more from WBRT treatment is predictable to a certain degree. Multimodality treatment (IT + RT + Systemic) was another factor. Group1 received more triple modality treatment than group2 (55% vs 33%). Multiple studies report synergistic effect when you combine multiple treatment modalities. Systemic chemotherapy and targeted therapy help eradicate disease in systemic sites that IT cannot reach due to blood brain barrier. Also, RT can provide deeper penetration into CNS tissue compared to IT whose penetration is limited to about 2-3mm [48]. Extent of metastasis to other organs also played significant role whether patients would experience survival benefit or not from the WBRT.Group1 had substantially lower systemic metastasis compared to group2 (46% vs67%). Explanationfor such results align with KPS score. Low KPS score often correlate with more extensive systemic involvement [49]. Hence it is not surprising that factors contributed to WBRT survival benefitincluded both KPS score and severity of systemic involvement with statistical significance.

For LMC patients with NSCLC primary, ten studies were identified. Factors that showed statistical significance with WBRT survival benefit were KPS score, WBRT, IT chemotherapy, and EGFR-TKI treatment. KPS score and IT chemotherapy share the same rationale with breast cancer patients. For the past decade, use of EGFR-TKI for NSCLC whose mechanism involves activating mutations in exons 19 and 21, has shown substantial survival benefit

[39,40,50]. When EGFR-TKI is combined with WBRT, synergistic effects have been reported with survival benefit for patients with NSCLC with brain metastasis [51,52]. Study from Welsh et al., [51] showed increased survival by 11.8 months when treated with EGFR-TKI with WBRT. It is believed that WBRT injures the blood brain barrier and allows better penetration and higher concentration of EGFR-TKI agents into CNS parenchyma [43,53,54].

Conclusion

The role of RT and its survival benefit for LMC patients are reviewed. Factors that are associated with WBRT survival benefit are systemically derived and extensively discussed. Though multiple factors are identified, KPS score seems to be the single most important prognostic factor that governs the survival benefit associated with WBRT. Algorithms for LMC patients with breast or lung cancer are devised. Such algorithm can serve as a general guideline to assess patient profile that can potentially have survival benefit by receiving WBRT.

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