

Oncological Management of Medulloblastoma and New Viral Therapeutic Targets

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Abstract—Medulloblastoma (MB) is one of the most prevalent brain tumours among paediatrics. Although its management has evolved over time still there is need to find new therapeutic targets for MB that can result in less normal tissue toxicity while improving survival and reducing recurrence. This literature review is aimed at finding new potential therapeutic targets for MB focusing on viruses that can be used as potential targets for MB. The review also gives an over-view of management of paediatric Medulloblastoma focusing on Radiotherapy management.

Keywords—Cytomegalovirus, Measles Virus, Medulloblastoma, Radiotherapy.

I. INTRODUCTION

MEDULLOBLASTOMA (MB) arises from the posterior fossa (PF) of the brain [1]. It accounts for 25% of all childhood brain tumours and 1% of adult primary brain tumours [2]. It constitutes 40% of posterior fossa tumours [3]. More than 70% of cases are seen in children below 10 years of age, 20% cases are seen in those less than 2 years of age and it is rare beyond 5th decade of life [3]. The peak age is 5 years and there is slight male predominance 1.3:1 [4]. Survival rates for children with medulloblastoma have increased over the past 30 years due to better surgery, the utilization of prophylactic cranio-spinal irradiation (CSI) and administration of chemotherapy [5]. It has high propensity for metastatic spread via cerebrospinal fluid (CSF) and has high radiosensitivity [6]. Given that it is very radiosensitive and accounts for a large number of paediatric brain tumours there is a need to minimize the toxicity and long term effects of treatment without jeopardizing its efficacy. The aim of this assignment is to critically review literature concerning the management of paediatric medulloblastoma focusing on the role of radiotherapy in the treatment of the disease. However it will include a general overview of diagnosis, staging and prognostic factors. The secondary aim is to describe emerging new therapeutic targets for MB especially focusing of role of some viruses as new therapeutic targets.

II. CLINICAL CHARACTERISTICS OF MB

This section will briefly describe the types of MB, staging, diagnostic work for Medulloblastoma.

A. Types of Medulloblastoma

WHO Histopathological classification based on morphology categorizes MB into desmoplastic,

medulloblastoma with extensive nodularity, classic medulloblastoma, large cell and anaplastic MB [7]. According to a consensus conference in Boston in 2010 molecular Classification of MB is divided it into 4 major transcriptional sub groups namely, Wnt, Shh, Group 3 and Group 4 [8]. These molecular sub grouping will help in determining target cohorts for certain drugs and also predict clinical outcome at the time of diagnosis [9].

B. Diagnostic Work-Up

Diagnosis is made by pre-operative MRI scan of the brain and spinal cord. As MB is more prone to spinal seeding a MRI imaging of the spine before surgery of primary tumour is important to avoid confusion with postoperative reactive meningeal enhancement that may mimic tumour involvement [10].

C. Staging

Staging for MB includes postoperative MRI of brain and spine along with CSF cytology from a lumbar puncture. These should be done within 72 hours of surgery to assess the degree of resection and residual disease [3]. With the use of either cytology or spinal MRI alone, leptomeningeal dissemination would be missed in approximately 14-18% of patients with medulloblastoma [11].

Staging helps stratifying patients (≥ 3 years of age) with MB into average risk and high risk groups. This in turn helps in selecting appropriate treatment for the patient. Average risk patients are those who at the time of diagnosis has non disseminated tumours and residual tumour $< 1.5\text{cm}$ on postoperative CT or MRI scan whereas high risk patients are those with metastatic disease (M) at the time of diagnosis and residual tumour $\geq 1.5\text{cm}$ and age less than 3years [12]. These days a modified Chang staging system is used to stage MB proposed by Langston based on surgical and postoperative imaging data. Phi and colleagues [13] also propose modified Chang's staging for metastatic staging and termed this approach CSF M staging in which within the cranial seeding occupies a higher rank than spinal seeding [13].

D. Prognostic Factors

Prognostic factors play an important role in the management of paediatric medulloblastoma by determining the risk of recurrence, metastatic spread, disease free and overall survival. The current consensus is that metastatic disease; postoperative residual disease more than 1.5cm^2 and age < 3 years are the worst prognostic factors [2]. In a multivariate analysis of 105 cases of childhood PNET tumours Michiels and colleagues [14] found presence of metastases

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and radiation dose as important prognostic factors. In a study by Jenkins and Colleagues [15], the 5 year survival rate for patients with M2 and M3 disease was 21% compared with 78% for patients with M0 and M1 disease.

A study involving paediatrics and adult patients with medulloblastoma showed that complete resection of MB, followed by cranio-spinal irradiation give rise to long survival rates in both children and adults. Delayed start of CSI was associated with poor outcome where as desmoplastic histology was associated with improved outcome [16]. Fourty seven patients were given chemotherapy out of which 21 patients received chemotherapy prior to CSI. The use of chemotherapy did not enhance survival [16]. Overall survival was 73%, local progression free survival was 62% and distant progression free survival was 77% at 60 months. The median CSI dose was 35.5 Gy with PF boost up to 54.0 Gy [16]. It seems that chemotherapy may be more effective if given after CSI irradiation or concurrently with RT rather prior to RT.

A retrospective analysis of survival of 103 children with primary brain tumours with 38% of patients having MB or PNET tumours reported the 5 year survival post diagnosis to be 84% for low grade Astrocytoma and 51% for MB and PNET and 33% for ependymomas [17]. The prognostic factors for overall survival were surgery where complete resection carried a Hazard ratio of 0.5, histopathological type with high grade Astrocytomas and Ependymomas carrying a hazard ratio of 3.7 and 3.9 respectively and RT (Hazard ratio of 0.5 for patients receiving RT). Treatment with RT was an independent prognostic factor for patients with MB and PNET i.e. such patients had a better prognosis if they undergo RT than High grade Astrocytoma patients [17]. Histology based 5 year Progression Free Survival of 82% for desmoplastic and MBEN, 78% for classical MB and 44% for anaplastic or large cell variants have been reported in MB patients [18].

Molecular markers such as STK15 (Kinase protein), TRKC (Neurotrophic Tyrosine Kinase Receptor Type 3) mRNA expression, CTNBN1 (Cadherin associated B-1Transcription factor protein) have been shown to improve response to Vincristine and Lomustine, chemotherapeutic drugs [19]. MB cells expressing high levels of CATNNB1 were sensitive to killing effect of Vincristine. MB cells expressing high levels of TRKC mRNA were correlated with killing effect of Lomustine [19]. Authors conclude that STK15, CTNBN1 and TRKC are vital genes for predicting the response of MB cells to treatment with Vincristine and Lomustine [19].

Another study also showed that CATNNB1 status is linked to improved outcome in childhood medulloblastoma [20]. STK 15 is shown to be an independent predictor of survival by Neben and colleagues [21].

A retrospective study carried out in China involving 173 MB patients (118 children and 55 adults) showed that post operative primary chemotherapy significantly effects the survival of classical MB, SHH group and WNT subgroup but did not influence desmoplastic and non SHH/WNT groups of MB. Post-operative primary RT was found to be a strong prognostic factor influencing the survival in all histological and molecular subgroups [22]. Therefore oncologists should

start using these molecular sub group classifications routinely in clinical settings.

III. MANAGEMENT OF MEDULLOBLASTOMA

Management of the disease is dependent on the current stage of prognosis and involves all 3 major modalities of treatment – surgery, chemotherapy and radiotherapy. Management will be discussed for average risk and high risk patients with MB. Discussion is restricted to the management of children \geq 3years of age as in infants radiotherapy is delayed to avoid deleterious effects of radiation [5].

A. Surgery

The first step in the management of MB is surgery which should be as radical as possible. This is because extent of surgery based on post resection imaging is an important prognostic factor in children $>$ 3 years of age and M0 disease [23]. The gross total resection; complete or near total resection is associated with improved disease control [1]. In a retrospective analysis of 149 patients with MB Khafaga and colleagues [24] showed that clinical and radiological complete resection of tumour at surgery resulted in significantly better survival than patients with incomplete tumour removal.

B. Radiotherapy

The role of radiotherapy in the management of MB will be discussed since surgery alone fails to control leptomeningeal disease [3]. The risk of CSF spread is 10% to 15% at diagnosis [1]. Postoperative irradiation is recommended for almost all patients with medulloblastoma. Bomford and Kunkler [6] propose that until recently in UK standard therapy for MB was postoperative cranio-spinal irradiation of 35Gy and a boost of 20Gy to the primary site. Using such doses various studies have reported that a 5 year overall survival of 63%-70% is routinely achieved [25], [26]. However it is important to note in the study by Sun and colleague MB patients had surgery followed by post-operative RT. Protracted RT course influenced DFS, stage impacted OS and DFS and RT dose affected OS and PFS [26].

In the study conducted by International Society of Paediatric Oncology and United Kingdom Children's Cancer Study Group M0-M1 MB patients received post-operative carboplatin based combination chemotherapy followed by RT [25]. The study reported 5 years Event Free Survival of 67.0% and OS of 70.7%. Patients completing RT within 50 days showed significantly better OS and EFS than those taking longer than 50 days. Use of chemotherapy and RT duration were predictors of better EFS [25].

PNET 3 study protocol recommend dose of 35Gy to craniospine in 21 daily fractions of 1.67Gy with a boost of 20Gy in 12 daily fractions of 1.67Gy with a total RT dose of 55Gy in 33# to Posterior Fossa (PF) [27]. According to this Protocol the dose to the head is specified at the mid plane of the central axis and for spine to the anterior spinal cord on the central axis. The RT dose to PF is specified at the mid plane of the central axis of the PF volume [27]. Paulino [3] state that for many years standard prophylactic cranio-spinal RT

(CSRT) dose for M0 disease has been 36 Gy and 38-40Gy for patients with M+ disease with tumour boost delivering a total dose of 45 to 50Gy.

The aim of the management is to improve survival and decrease the long term consequences of treatment. One strategy is to use low dose cranio-spinal irradiation with chemotherapy for standard risk disease (M0) [28].

Packer and colleagues [29] state, a 79% 5 year Progression Free Survival (PFS) in children between 3 and 10 years old with M0 MB disease when treated with reduced dose RT (23.4Gy) combined with concurrent Vincristine and subsequent Cisplatin based combination therapy. The overall survival (OS) rates compared favourably to those obtained in studies using full dose RT alone or RT plus chemotherapy. This study suggested that for non disseminated MB low dose Cranio-spinal Irradiation given concurrently with chemotherapy and followed by adjuvant Chemotherapy is a viable approach.

Paulino [3] state that for non metastatic disease most radiation oncologists now use lower cranio-spinal doses with combination chemotherapy in children in order to reduce long term sequelae.

Another strategy is to use reduced dose postoperative RT alone. According to one prospective randomized study Cranio-spinal RT dose less than 36Gy without adjuvant chemotherapy resulted in poor survival and increased relapses in low risk patients [30].

A cranio-spinal dose lower than 23.4Gy for standard risk medulloblastoma has also been reported in the literature. A pilot study by Jackacki and colleagues [31] showed 57% 5 year Progression Free Survival (PFS) rate with the use of 4 months of pre irradiation chemotherapy followed by 18Gy of CSI with standard boost to PF in children with M0 disease. Despite low CSI dose significant long term neurocognitive deficits were observed (due to PF boost) along with exo-primary relapses. Freeman and colleagues [32] after analyzing a number of different trials for children with MB concluded that low dose CSI (23.4Gy) and Chemotherapy cause a significant improvement in DFS and OS in patients with average risk disease. This is now the standard treatment for average risk patients.

C. High Risk Disease

Metastatic medulloblastoma is associated with high risk of neuraxis relapse and therefore require more aggressive treatment [3]. RT doses less than 30Gy to whole brain result in increased supratentorial relapses in children with M+ medulloblastoma [33]. The standard management of M+ disease is High dose chemo radiotherapy [3], [32]. It is currently believed that adjuvant chemotherapy is beneficial compared to neoadjuvant chemotherapy especially in patients with high risk of recurrence [2]. This is because it avoids delaying postoperative RT which is associated with increased relapse rates by a number of studies.

IV. RADIOTHERAPY TECHNIQUE

A. Simulation

The Cranio-spinal RT setup and immobilization details vary among treating centres. Craniospine is frequently simulated using fluoroscopy. However CT simulation can also be used to plan cranio-spinal therapy. CT simulation offers increased speed hence reduced immobilization time compared to conventional simulation [34]. It also results in improved accuracy in field placement and localization of critical organs and target volume.

B. Position and Immobilization

Prone position with a head immobilizing cast or vacuum device (usually a Perspex head shell) has been traditionally used to administer CSI [1]. Prone position allows direct visualization of the cranio-spinal junction and junction between upper and lower spinal fields thus avoiding overlap between matching fields. Disadvantages of prone position include reduced reproducibility of cranial field and are uncomfortable for patients. A study by Chang and colleagues [35] utilized CT planned supine cranio-spinal technique and the use of rigorous film verification. This study reported reduced systemic error compared to conventional prone technique but increased stochastic error of spine setup.

C. Clinical Target Volume and Field Arrangement

1. Cranial-Spinal Fields

For CSI the CTV includes whole brain and whole length of spinal axis covering meninges [12]. For the cranial fields it is important to treat adequately the region of cribriform plate and the inferior temporal lobes of the brain as inadequate coverage of cribriform plate may lead to sub-frontal and sub temporal recurrences as documented by a retrospective study of 77 patients with MB conducted by Miralbell and colleagues [36]. The brain and upper cervical spine is usually treated with 2 lateral opposed fields and the rest of the spine with one or two posterior fields [37]. The cranial field is matched to the posterior spinal field and divergence of fields is corrected by rotating the collimator angle and couch angle [1]. A moving junction technique further prevents under or over dosage at cranio-spinal junction [1]. The placement of cranio-spinal junction is crucial in terms of the dose to cervical spinal cord and surrounding organs. A study by Narayana and colleagues [38] showed that the use of lower junction in the neck (C5-C7) resulted in lower dose to surrounding organs such as mandible, oropharynx and thyroid gland in contrast to a high junction (C1/C2 vertebrae). However, high junction resulted in reduced dose to cervical spinal cord. Hence a low cranio-spinal junction is usually preferred.

Traditionally S2/S3 is used as inferior border of lower spinal field however a retrospective study by Scharf and colleagues [39] revealed that thecal sac termination in 8.7% cases to be below S2-S3. Hence use of MRI is recommended to determine the inferior border of spinal field.

2. Posterior Fossa Boost

The posterior fossa boost is typically designed to encompass the entire infra-tentorial compartment [1]. Different techniques are used to treat posterior fossa. Traditionally PF has been treated using parallel opposed lateral beams and has relied on bony landmarks [3]. Besides, 3DCRT – 3 dimensional conformal RT has also been used to treat the entire PF in order to spare the cochlea. A study by Paulino and colleagues, [40] compared 3 different techniques of delivering the posterior fossa boost in patients with medulloblastoma. Technique A used parallel opposed lateral fields (2D RT); Technique B (3DRT) utilized a pair of coplanar posterior oblique beams whereas Technique C (3DRT) utilized a pair of posterior oblique fields and a vertex field. This study showed the superiority of 3DCRT over 2DRT. With 3D conformal RT entire target volume is treated without any under or over estimation of PF and dose to cochlea and pituitary is minimized. This study recommended the use of Technique B for PF boost as it encompasses entire target volume, spares cochlea (50% of the prescribed dose) and non PF brain and may result in better quality of life

3. Borders

Borders for PF includes anterior border at posterior clinoid, inferior border at C1/C2, post border encompasses posterior skull. The definition of superior border has been inexact and is usually taken as 1cm greater than half the distance from foramen magnum to the vertex [3].

4. RT Treatment Factors

In a multivariate analysis Paulino and colleagues [41] reported that a RT course of > 50 days and PF dose < 50Gy resulted in low progression free survival rates. A delay of initiation of RT also results in inferior outcome as reported by Hartsell and colleagues [42] and German HIT trial [43].

Advances in RT has resulted in use of Intensity Modulated Arc Therapy PF boosts to achieve volume reduction in the PF from high dose RT without experiencing excess marginal disease recurrence, to achieve excellent local control [44] and to reduce ototoxicity [45], [46]. Other techniques such as SRS and VMAT are also been studied.

A retrospective planning study comparing 3D CRT, VMAT and Helical Tomotherapy (HT) for CSI in paediatric patients (66.7% were MB and PNET patients) found that VMAT generates dose distributions that have higher possibility to spare involved Organs at Risk while controlling the tumour [47]. The same prescription (i.e. a total dose of 23.4 Gy) was prescribed in all cases to facilitate inter-comparison between all patients [47]. The study also showed that VMAT plans had the highest probability of benefit while keeping the lowest probability of injury compared with other two techniques i.e. a larger range of prescription dose can be given without causing excess in the probability injury. There was a significant increase in the tumour control probability without causing severe injury to normal tissues for both IMRT and VMAT compared to 3DCRT technique (P=0.01 for VMAT vs. 3DCRT and P=0.01 for Helical Tomotherapy vs. 3DCRT).

This study has shown that in future instead of using standard prescribed dose levels (usually derived from literature review) to the target optimal dose prescription can be calculated using radiobiologically driven methods [47]. To tackle the problem of large low dose region produced by VMAT and HT alternative planning methods such as partial arcs can be used to reduce the risk of developing secondary cancers [47].

V. CHEMOTHERAPY

Chemotherapy is used in a number of settings. It is used as part of initial treatment of high risk disease and standard risk disease in combination with low dose CSRT as discussed above. It is also used in the treatment of infants to delay radiotherapy and in the event of recurrence as salvage therapy [48]. There is no consensus on optimal chemotherapy regimes.

VI. TOXICITY

The RT side effects include both acute and long term sequelae. Acute side effects of irradiation to brain and spinal cord include nausea and vomiting, headache, alopecia (baldness), Fatigue, somnolence, tracheal irritation, oesophagitis, myelosuppression and skin reaction [49]. Hopkins and colleagues [49] further suggest that these side effects are managed with the use of antiemetics, pain control, rest, steroidal therapy, use of fluids for oesophagitis and skin care teaching (use of moisturizing cream or 1% hydrocortisone) and with proper nutritional advice. In addition children are advised to keep the treated area covered (especially the head) when out in the sun for at least a year after the treatment.

The late RT side effects include neurocognitive, neuroendocrine sequelae, cataracts, second malignancy, hearing loss, defects in spinal growth, infertility, and gonadal dysfunction [50]. Growth hormone (GH) deficiency is the predominant neuroendocrine sequelae whereas gonadotropin dysfunction and hypothyroidism is observed less frequently [51]. [GH deficiency can be treated with Growth Hormone therapy and an endocrine referral is usually done to monitor and manage endocrine sequelae [52].

Main neuropsychological complications include impairment in speed processing and organization abilities resulting in low IQ scores in children treated for PF tumours as reported by Grill and colleagues [53]. Jackacki and colleagues [31] reported neurocognitive sequelae mainly in attention and concentration areas. This study has also reported that high CSRT dose and large radiation volume increases neuropsychological sequelae. Another study involving child survivors of MB with average risk and high risk patients getting 23.4Gy CSI, 36-39Gy CSI respectively and adjuvant Chemotherapy reported verbal memory outcomes below the population average and attention deficits [54]. A study conducted in Japan to assess long term effects of CNS Irradiation in a monozygotic twin girl reported shorted spine and upper and lower limbs than the control subject. The patient received post operative chemotherapy, CNS irradiation with 47.8Gy directed to PF, 30.2Gy to cerebral hemispheres,

and 20Gy to whole spine. Low intellectual ability was reported and cognitive dysfunction did not improve even after 6 years post treatment. High Thyroid stimulating hormone levels were reported although the Thyroid hormone level was normal. This study concluded that treatments causing no late toxicity need to be pursued [55].

One way to reduce these late complications is by lowering the boost volume from the entire PF to the tumour bed. Douglas and colleagues [28] reported excellent disease control (86% survival rate) with conformal tumour bed boost in combination with chemotherapy and reduced dose CSI in average risk MB. However the improvement in late complications awaits further confirmation. Other techniques such as IMRT, hyper-fractionated RT (HFRT) and protons can be used to reduce radiation induced toxicity and are currently under investigation. A retrospective study by [56] Huang and colleagues [46] reported a significantly lower rate of grade 3-4 ototoxicity in patients treated with IMRT boosts compared to the patients treated with conventional RT. HFRT significantly reduces the incidence of primary hypothyroidism than conventional fractionated RT in treatment of CNS tumours [56]. Mulhern and colleagues [57] recommended use of behavioural remediation and pharmacotherapy (with methylphenidate) to avoid potential neurocognitive deficits.

VII. NEW THERAPEUTIC TARGETS FOR MB

A New treatments for MB needs to be explored not only because current treatment modalities such as surgery, radiotherapy and chemotherapy are associated with debilitating side effects but also because at least 1/3 of the MB patients remain refractory to conventional treatments [58]-[60]. This section will briefly describe emerging potential targets for MB.

A. Human Cytomegalovirus (HCMV) as a New Therapeutic Target

Studies have shown that 92% of primary MB tissue samples and MB cell lines are infected with HCMV proteins [61]. Disruption of neuronal differentiation into neurones and astrocytes could lead to development of brain tumours [62], [63]. There is also evidence that HCMV exists in neuronal stem cells and therefore this infection of HCMV of tumour progenitor cells can lead to development of MB via HCMV specific effects of tumourgenesis, inflammation and immune avoidance strategies [64].

The HCMV is capable of inducing and enhance COX-2 expression into MB cells as well as enhancing production of PGE2 (an inflammatory mediator) through viral US28 protein [61]. The virus is also capable of inducing STAT3 phosphorylation, vascular endothelial growth Factor (VEGF), IL-6 and inflammation and tumour formation in vivo [65]. The US28 protein encourages development of dysplasia and cancer especially during inflammation phase. The virus induces expression of COX2 and 5-lipo-oxygenase which in turn cause production of prostaglandins and leukotrienes that are responsible for inflammation. Thus both COX2 and PGE2 cause tumour progression by stimulating cell proliferation,

promote angiogenesis and invasion, prevent apoptosis and repress immune responses [66]-[68]. The antiviral drug valganciclovir and COX-2 inhibitor celecoxib prohibited HCMV replication in vitro and prevented PGE2 production and reduced MB tumour cell growth both in vitro and invivo [61]. This HCMV have a potential to be used as therapeutic target in HCNV positive MB tumours.

HCMV is considered onco-modulator not oncogenic by some researchers [69]. Onco-modulation is described as a process in which virus may infect the tumour cells and supports tumour progression and enhance and modulate their malignancy in a manner not involving direct transformation [70]. Long term persistent infection is vital for the virus to demonstrate its onco-modulatory effects resulting in increased malignancy in terms of increased tumour proliferation and metastasis [70]-[73] by exploiting tumour environment characterized by disturbed intracellular signalling pathways, transcription factors and tumour suppressor proteins [69]. Clinical findings have shown that glioblastoma patients with less HCMV-infected cells survived twice as long as patients with more HCMV infected cells thereby signifying that HCMV infection of tumour cells is capable of changing the disease course in this patient group [74]. COX2 expression results in PGE2 production which in turn leads to angiogenesis, restrained apoptosis and innate immunity thereby enhancing tumour progression [75].

Microsomal PGES-1 (mPGES-1), another membrane bound protein like COX-2 has been shown to be over expressed in some tumours [76]. Its expression is strongly induced by inflammatory mediators like COX-2 and is also considered a therapeutic target for these cancers. Induced expression of mPGES-1 leads to tumour proliferation, metastasis, angiogenesis and resistance to apoptosis. Its potential role in MB needs to be explored.

15-PGDH is an enzyme that inactivates PGE2 [77]. Reduced 15-PGDH expression was noted in different cancers such as colorectal, breast, prostate, lung, thyroid, gastric and pancreatic cancers and has been associated with tumourgenesis and cancer progression [78]-[81]. It is therefore considered as a tumour suppressor. The expression of 15-PGDH in MB and its role as therapeutic target for MB needs to be explored.

B. Recombinant Oncolytic Measles Virus (MV)

An oncolytic virus is able to infect and destroy tumour cells leaving the adjacent normal tissue undamaged [82]. Studies have shown the efficacy of measles oncolytic virus in MB mouse models. Administration of Measles virus into the tumour lead to either stabilization or remission of tumour and also increased median survival time of treated mice [83], [84].

Another study investigated the effectiveness of angiogenesis inhibitor equipped Measles Virus in MB cells and MB infected mouse models [85]. This study has shown decreased tumour associated angiogenesis and trends for improved survival in mouse models. Media obtained from infected cells showed inhibition of multiple angiogenesis

factors. The study concluded that oncolytic MV armed with angiogenesis inhibitors have a therapeutic benefit [85].

VIII. CONCLUSION

Management of MB has evolved in recent years. Management includes maximum resection of the primary tumour and cranio-spinal radiation and chemotherapy. Combination treatment is now the standard treatment for average risk patients involving low dose CSI (23.4Gy) with a boost to entire PF (total dose 54-55Gy) along with chemotherapy on the grounds that a lower dose of CSI results in fewer long term effects. High risk patients are treated with high dose chemotherapy and CSI (38-40Gy) with a boost to entire PF. It is generally believed that it is important to deliver postoperative RT without any delay. Both acute and long term RT side-effects are being reported. New RT techniques such as IMRT including arc therapies (VMAT and Helical Tomotherapy) have resulted in reduced side effects. The final aim is to develop biologically driven RT treatments and risk-based strategies that include appropriate combinations of chemotherapy with irradiation in order to maximize the cure rate for all patients while reducing long term complications of therapy. Cytomegalovirus and Measles Virus may be effective therapeutic targets for MB. Their potential role as new therapeutic targets for MB needs to be further explored.

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