

Leukemia and the Nervous System

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Abstract

Leukemia affects both the central and peripheral nervous system. Neurological complications are a consequence both of direct leukemic infiltration as occurs with leukemic meningitis and due to complications of either anti-leukemic treatment (thrombocytopenic or DIC-related intracranial hemorrhage, steroid myopathy, vinca alkaloid peripheral neuropathy) or immune compromise (*Herpes zoster* shingles or *Aspergillus* meningitis).

Introduction

Leukemia is classified into acute and chronic types, and further separated into lymphoid and myeloid and whether tumors are comprised of cells that appear mature (chronic leukemia) or immature (acute leukemia) ¹⁻³. Within each category, distinct leukemia's are defined according to a combination of morphology, immunophenotype and cytogenetic features in addition to clinical syndrome. An estimated 30,800-33,400 new cases of leukemia will be diagnosed in the United States this year. Acute leukemia, a clonal disease of hematopoietic stem cells, account for slightly more than half of all new leukemia's in the United States annually. Hematopoietic stem cells may differentiate along lymphoid or myeloid lines. Acute myelogenous leukemia (AML), also called acute non-lymphocytic leukemia, is three times more common than acute lymphocytic leukemia (ALL), represents 60-70% all acute leukemia and 11,000-12,000 new cases occur annually in the United States. AML is most common in individuals older than 50 years of age whereas ALL is more common in children and young adults. Approximately one third of patients with either ALL or AML achieve long-term survival however outcome is highly dependent upon cytogenetic profile. Chronic lymphocytic leukemia

(CLL) is the second most common adult leukemia and affects 8,000-9,000 persons in the United States annually. Like AML, CLL is more common in the elderly. CLL represents a monoclonal disorder with expansion of small lymphocytes of B-cell (95%) or T-cell (5%) lineage. Median survival is six years but is dependent upon staging (as per the Rai staging system) at disease presentation. CLL only rarely progresses to a more malignant phenotype. Chronic myelogenous leukemia (CML) is characterized by excessive clonal proliferation of myeloid cells and affects 4,000-5,000 adults annually in the United States. The disease can be divided into two phases, an initial chronic phase in which cell maturation is normal followed by an acute phase (blast crisis), characterized by maturation arrest. Median survival of CML is four years.

The neurological manifestations of leukemia are diverse and reflect either direct tumor involvement or indirect complications of immunosuppression or therapy. The following discussion of the neurological complications of leukemia amplifies that outlined in Table 1.

Leukemic parenchymal tumor

AML may give rise to solid tumors consisting of myeloid leukemic blasts called granulocytic sarcomas or chloromas⁴⁻⁶. The term chloroma results from the greenish color of these tumors caused by the presence of myeloperoxidase. Chloromas usually have a dural attachment although parenchymal tumors have rarely been reported. These tumors are hypercellular and avidly enhance with either cranial MR or CT. Neurologic findings are dependent upon location. Chloromas most often occur in bone that may result in epidural spinal cord compression, the orbit that may result in proptosis and a restrictive ophthalmopathy, or dura, which may simulate a meningioma. Chloromas are

very radiosensitive however their presence typically heralds aggressive systemic disease such that disease control is a function of extracranial therapy and response.

Intracranial hemorrhage

Hemorrhagic complications are common in patients with acute leukemia (approximately 20%) and constitute the second most common cause of death in such patients (20% of all leukemic deaths result from intracranial hemorrhage) ^{4,7-15}.

Intracranial hemorrhage (ICH) is the most common hemorrhagic complication in acute promyelocytic leukemia and is not infrequent in AML and ALL (ranging in occurrence from 2-18% of all patients with acute leukemia). ICH may occur at time of diagnosis (early hemorrhage) or subsequent to diagnosis and following initial treatment (late hemorrhage). Disseminated intravascular coagulation (DIC), disseminated aspergillosis or mucormycosis, leukemic cell infiltration, thrombocytopenia or l-asparaginase chemotherapy-related in that order, are the most common etiologies for ICH. Both DIC (especially common in the M3 subtype of AML) and thrombocytopenia typically result in a solitary often-massive ICH whereas disseminated fungal infection and ICH occur during neutropenia and is a result of hemorrhagic infarction. Leukemic cell infiltration occurs with marked leukocytosis (defined as >300,000 leukemic cells/ L) and results in multiple intracranial hemorrhages. L-asparaginase may induce hyperfibrinogenemia and result in cortical vein or sinus thrombosis with resulting venous infarction. Fungal-related mycotic aneurysms and ICH and would be a consideration in a patient with blood culture positive for fungus. Topographically the majority of ICH is intraparenchymal with cerebral hemorrhage more common than cerebellar. Subdural hematoma is relatively infrequent except as a complication following stem cell transplantation. Aside from

symptomatic treatment of ICH, treatment is directed at the underlying cause of hemorrhage (for example correction of an underlying coagulopathy, whole brain irradiation or systemic chemotherapy for hyperleukocytosis and brain leukemic infiltration). In general, ICH in the patient with leukemia portends for shortened survival.

Encephalopathy

A variety of etiologies may account for encephalopathy (defined as an alteration in consciousness, neurobehavioral abnormalities, seizures or focal neurological deficits) in the leukemic patient. Most commonly, toxic/metabolic (narcotic overmedication, hyponatremia, uremia, organ failure) causes are identified however consideration of DIC, sinus thrombosis, ICH, chemotherapy-related (either high dose methotrexate or cytarabine), radiation-related and infectious (disseminated *Candida* or *Aspergillus*) is necessary^{4,7-15}. Evaluation for DIC is warranted in any patient with leukemia and encephalopathy and should include a coagulopathy screen. Sinus thrombosis is occasionally due to leukemic infiltration of the superior sagittal sinus but more often occurs with dehydration, sepsis-related coagulopathy or l-asparaginase chemotherapy. Clinical presentation may be as an isolated headache, raised intracranial pressure syndrome (headache, nausea, vomiting, transient visual obscurations, diplopia), hemiparesis or encephalopathy. Cranial imaging most often demonstrates a venous hemorrhagic stroke. Chemotherapy-related encephalopathy is seen following high-dose methotrexate as either a transient diffuse encephalopathy or occasionally as a posterior reversible leukoencephalopathy defined best by cranial MR with posterior quadrant white matter high signal abnormalities. High-dose cytarabine (ara-C), used in the treatment of AML, causes either a pure cerebellar syndrome or diffuse encephalopathy and is more

common in the elderly patient (age > 60 years) in association with renal impairment. Radiation-related encephalopathy occurs in two contexts, as an early-delayed side effect or more commonly, as a late-delayed radiation complication^{4,12,16}. In both instances, radiation therapy is given as prophylactic whole brain radiotherapy in high-risk (for leukemic meningitis) patients. Early-delayed radiation complication, occurring weeks after completion of radiation therapy, is a generalized demyelinating syndrome that presents with hypersomnolence, is benign and resolves with steroid treatment. Late-delayed radiation complication (occurring years after radiotherapy) has two major forms, mineralizing arteriopathy and a necrotizing leukoencephalopathy. The former is reflected as dystrophic calcification in small blood vessels and is commonly seen in the basal ganglia, dentate nuclei, thalami and subcortical white matter. Necrotizing leukoencephalopathy is an admixture of demyelination, astrogliosis and necrosis presenting with either a static or progressive encephalopathy. Neither condition is treatable however may be related to both chemotherapy (in particular methotrexate, both systemic and intra-CSF) and radiation dose and therefore potentially modifiable as acute leukemia induction regimens are tailored to risk of CNS relapse.

Meningitis

Meningitis in leukemia may result from LM, subarachnoid hemorrhage, chemical (treatment-related following intra-CSF instillation of chemotherapy) or infectious (bacterial or fungal)^{4-6,10,11,13-15,17-23}. The presence or absence of LM always needs to be ascertained as if diagnosed, prognosis is profoundly affected. Subarachnoid hemorrhage occurs in the context of ICH, either in isolation or more frequently as more diffuse

hemorrhage secondary to DIC. Spinal subarachnoid hemorrhage may occur in the context of DIC and acute promyelocytic leukemia and present primarily with back pain that migrates rostrocaudally. Chemical meningitis (typically due to intra-CSF cytarabine or methotrexate and most often given intraventricularly) is temporally related to intra-CSF chemotherapy. Chemical meningitis begins one to two days after intra-CSF chemotherapy administration, is transient typically lasting less than five days and demonstrates no evidence of infection with CSF culture. Like other meningitic syndromes, patients complain of headache, fever, nausea, vomiting, photophobia and meningismus. Notwithstanding an inflammatory CSF, chemical meningitis rapidly abates and is mitigated by oral steroids. Infectious meningitis occurs in leukemia due to immunosuppression both as a result of the underlying disease and its treatment. *Listeria*, *Candida* and *Aspergillus* are common infectious etiologies however clinical presentation differs. *Listeria* presents as a meningitic syndrome whereas *Candida* presents with a diffuse encephalopathy and multiple small brain abscesses and *Aspergillus* presents with progressive hemorrhagic stroke confined to a single vascular territory.

Acute leukemia, in particular ALL, has the highest propensity to invade the meninges and result in leukemic meningitis (LM)^{12,14,17}. This is true in addition for Burkitt's lymphoma and lymphoblastic lymphoma (2-3% all adult NHL), two subtypes of what is now considered ALL⁶. Although AML infrequently results in LM, an unusual subtype, acute myelomonocytic leukemia (AMML) is at high risk (estimated at 20%) for the development of LM^{5,19}. Prior to CNS prophylaxis, 70% of autopsied patients with ALL had postmortem evidence of LM. However using contemporary induction protocols with CNS prophylaxis, only 5-10% of adult patients with acute leukemia develop CNS

disease^{14,15}. Nonetheless, patients who develop CNS recurrence with leukemia have a poor prognosis. Chronic leukemia (CLL and CML), the most common adult leukemia encountered, rarely causes LM^{10,11,18}.

Leukemic meningitis may be seen at diagnosis (3-5% all adult patients with ALL) or at relapse (5-7% of adult patients with ALL and prior CNS prophylaxis)^{13,17}. Three groups of patients with LM at relapse are recognized; CNS only (53%), bone marrow relapse followed by CNS (24%) and simultaneous CNS and bone marrow relapse (27%). In the series of Surapaneni of 527 consecutive adult patients with ALL, amongst patients with isolated LM, 88% subsequently relapsed in the bone marrow¹⁷. As a consequence, the presence of LM regardless of time of occurrence after induction therapy predicts for systemic disease recurrence and poor outcome. Therefore the treatment of adult acute leukemia increasingly utilizes CNS risk stratification and tailors CNS prophylaxis accordingly so as to prevent CNS relapse²⁴.

Risk for relapse of LM is associated with several prognostic factors in adults including young age, leukocytosis, presence of extramedullary disease, a high leukemia cell proliferation rate (S+GM fraction >14%), an elevated serum LDH level (>600U/L), mature B-cell immunophenotype (L3), Philadelphia chromosome positivity [t (9; 22)], CD56 expression by leukemia cells and an elevated serum β_2 -microglobulin level (>4mg/dl)²⁴⁻²⁹. Kantarjian utilized 3 risk factors (elevated serum LDH, elevated serum β_2 -microglobulin, and a high leukemia cell proliferation rate) in adult ALL and determined the risk of CNS relapse. Four groups were identified and in patients with one risk factor the risk of LM at one year exceeded 13% and increased to >20% if two or more risk factors were present. This approach has resulted in CNS disease risk

stratification and intensification of CNS prophylaxis in adult ALL in an attempt to mitigate the emergence of LM²⁴. Similar to data with lymphomatous meningitis, once LM has occurred prognosis is poor with median survival of six months¹⁷.

In ALL, patients with evidence of CSF leukemic blasts at diagnosis (3-5% of all patients with ALL), survival varies according to CSF category. CSF categories are as follows; normal CSF without blast cells (CNS1), normal CSF i.e. no evidence of pleocytosis (<5 WBC/microliter of CSF) and blasts (CNS2), CSF pleocytosis and blasts (CNS3), traumatic LP with blasts (TLP+), and traumatic lumbar puncture without blasts (TLP-)¹⁷. Patients with CNS1, CNS2 and TLP- have similar overall survival whereas patients with CNS3 have a markedly worse prognosis and overall survival. Patients with TLP+ have intermediate survival relative to CNS1/2 and CNS3. These data suggest two further groups of patients (CNS3 and TLP+) who may benefit from more aggressive CNS prophylaxis than that administered to CNS1 (and CNS2 & TLP-) patients.

The clinical presentation of LM in patients with leukemia is similar to that seen in patients with LM from solid tumors^{19,22,23,31}. However, patients with hematologic malignancies present with a higher frequency of cranial nerve signs (for example trigeminal neuralgia or optic neuropathies) as initial manifestations of neoplastic meningitis²⁰. LM is pleomorphic in its clinical presentation as it affects all levels of the CNS^{19,20,22,23,31}. In general, 3 domains of neurologic disturbance are characterized as affected by LM including; (1) the cerebral hemispheres, (2) the cranial nerves, and (3) the spinal cord and roots. The common symptoms of cerebral hemispheric dysfunction are headache and mental status change. Signs found in patients with LM and cerebral

hemisphere disturbance encompass mental status changes including confusion and dementia, seizures, and hemiparesis.

The single most useful laboratory test in diagnosing LM is an examination of the CSF usually obtained by lumbar puncture^{19,20,22,23,31,32}. In nearly all patients with LM, the CSF is abnormal regardless of the results of CSF cytology. CSF cytology positive for malignant cells is the standard method in most clinical series by which LM is diagnosed. Numerous biochemical markers have been evaluated but in general, their use has been limited by poor sensitivity and specificity³³⁻³⁹. In leukemia, monoclonal antibodies against cell surface markers can be used to distinguish between reactive and neoplastic lymphocytes in the CSF^{40,41}. Furthermore the demonstration by immunohistochemistry of monoclonality of CSF cells is as compelling as positive cytology. Lastly, the finding of CSF lymphocytes all of B-cell lineage is highly suggestive of LM as reactive lymphocytes in CSF are of T-cell lineage. Cytogenetic studies have also been evaluated in an attempt to improve the diagnostic accuracy of leptomeningeal metastases. Flow cytometry and DNA single cell cytometry, techniques that measure the chromosomal contents of cells, and fluorescent *in situ* hybridization (FISH), that detects numerical and structural genetic aberrations as a sign of malignancy, can give additional diagnostic information, but still have a low sensitivity⁴²⁻⁴⁴. Polymerase-chain reaction (PCR) can establish a correct diagnosis when cytology is inconclusive, but the genetic alteration of the neoplasia must be known for it to be amplified with this technique, and this is may be helpful with hematological malignancies⁴¹⁻⁴⁴.

A variety of neuroradiographic methods are available to evaluate patients with suspected LM including cranial computed tomography, brain and spine magnetic

resonance imaging, computerized tomographic myelography and radionuclide CSF flow studies⁴⁵⁻⁵⁰. Despite the superiority of cranial MR-Gd to CE-CT in the evaluation of LM, both studies have a high incidence of false negatives (30% by MR-Gd and 58% by CE-CT). Normal studies by either methodology do not exclude a diagnosis of LM in patients with negative CSF cytologies; however positive MR-Gd or CE-CT may both be suggestive and diagnostic of LM^{19,20,22,23}. In the majority of patients with LM, MR-Gd and CE-CT are most useful in demonstrating bulky disease, a pattern of disease most responsive to radiotherapy and least responsive to intra-CSF chemotherapy (see below) though less commonly seen with LM. Radionuclide CSF flow studies or so-called radionuclide ventriculography (FS) provide a safe physiological assessment of the functional anatomy of the CSF spaces^{23,50}. FS have in prior reports demonstrated superiority in detecting interruption of CSF flow in patients with LM when compared with CT-M and S-MR. However, FS are informative only with respect to compartmentalization of CSF and provide no information regarding bulky leptomeningeal disease, an aspect of LM best addressed by CT-M or S-MR. In addition, though infrequently demonstrated, CT-M and S-MR are clearly superior to FS in detecting epidural spinal cord compression or intraparenchymal spinal cord metastases, two CNS complications of metastatic systemic cancer requiring emergent radiotherapy.

Therefore patients suspected of LM should undergo: (1) 1 or 2 lumbar punctures for CSF cytology and if negative, proceed to either a ventricular or lateral cervical CSF analysis; (2) contrast enhanced cranial imaging (MR preferred to CT); (3) contrast enhanced spine MR in patients with spinal symptoms; and (4) CSF flow study either by lumbar or ventricular radioisotope administration.

Increasingly, the hematologic oncologist has adopted a risk-oriented approach to the prophylaxis of LM, with therapeutic regimens tailored to the risk of the individual patient. This approach is a reflection of the impoverished patient survival following the development of LM (2-6 month median survival) ²⁴.

A compilation of studies from adult patients with ALL and CNS prophylaxis treatment regimens suggest the following; regimens without cranial irradiation are effective, high-dose systemic therapy for low-risk disease is sufficient without intrathecal therapy, intrathecal methotrexate or alternating with cytarabine is effective without need for triple intrathecal therapy, intrathecal therapy and high-dose systemic chemotherapy are effective for high-risk disease and a risk-oriented approach is optimal. What however is optimal CNS prophylaxis for the high-risk patient remains problematic and under investigation?

The goal of treatment of LM is palliative and meant to improve or delay progression of neurologic symptoms and signs. The treatment of LM includes craniospinal irradiation, traditional systemic chemotherapy, intrathecal chemotherapy, and high-dose chemotherapy with hematopoietic stem cell rescue (Table 2). Since most CNS disease in ALL and NHL occurs in the setting of advanced or relapsed systemic disease, control of local or systemic disease is critical.

Epidural spinal cord compression

Leukemic epidural spinal cord compression (ESCC) is relatively rare (1% occurrence) with two exceptions, Burkitt's lymphoma and lymphoblastic lymphoma (incidence 10-18%) both of which are presently considered as part of the ALL spectrum and similarly treated ^{4,6,15}. Unlike solid cancers that initially metastasize to the vertebral body, leukemic

ESCC originates in the paravertebral space and extend through the intervertebral foramina with resultant cord compression. As a consequence, bone involvement by neuroimaging is absent. Additionally, unlike solid cancer, there are no issues of spinal instability due to the lack of vertebral body involvement. Otherwise the presentation of leukemic ESCC is similar to that commonly seen with lymphoma and solid cancer beginning with pain (local, referred or radicular) and evolving to myelopathy. Surgery is rarely contemplated (unless the primary is unknown) as leukemic ESCC is exquisitely radiosensitive and additionally to responds to systemic chemotherapy. The later approach however is reserved for patients with pain only ESCC syndromes. Most importantly, the presence of ESCC in patients with leukemia does not negatively affect survival as treatment most often results in complete tumor eradication. Two other considerations in leukemic patients with ESCC include an epidural hematoma seem most often in the thrombocytopenic patient following a lumbar puncture or in the patient on chronic steroids wherein steroid induced epidural lipomatosis may occur.

Radiculopathy

Herpes zoster is a common cause of dermatomal vesicular rash in leukemic patients and is most common in CLL where 7% of patients have at least one *Herpes zoster* infection during the course of their disease^{4,5,10,11}. Most problematic of acute *Herpes zoster* is an acute pain syndrome that may evolve into post-herpetic neuralgia, a chronic pain syndrome. Dissemination may occur in up to 20% during which neurological involvement is seen in 50%. Neurological manifestations occurring in the context of disseminated *Herpes zoster* may include encephalitis, meningitis and motor neuropathies.

Peripheral neuropathy

Neuropathies occur in two contexts in leukemia, direct tumor infiltration and as a consequence of chemotherapy^{4,12}. Optic neuropathy either unilateral or bilateral is a common presentation of LM (incidence 20-30%) and warrants emergent radiotherapy to preserve vision. Another common cranial neuropathy involved in the context of LM is the numb chin syndrome wherein leukemic cells preferentially affect the mental nerve, a subdivision of the mandibular branch of the trigeminal nerve. Either neuropathy in a leukemic patient is an indicator of LM and warrants LM-directed therapy. The most common peripheral neuropathy that occurs in leukemic patients is a length dependent axonal sensorimotor neuropathy caused by vinca alkaloids. Initial symptoms are paresthesias of the hands and feet followed by progressive motor dysfunction culminating in foot and wrist drop. Occasionally, symptoms may be transiently worsened by administration of granulocyte- or granulocyte macrophage colony stimulating factor. Though the neuropathy may resolve after drug discontinuance, early dose modification based on clinical symptoms and signs mitigates the development of a disabling chronic neuropathy. Cranial neuropathies though uncommon may occur and affect oculomotor, trigeminal, facial or recurrent laryngeal nerves manifested as ptosis, diplopia, jaw pain, facial paresis and vocal cord paralysis. Lastly, transient autonomic neuropathy is common (20-30% of patients) with vinca alkaloids typically seen as abdominal pain with constipation. Rarely in patients treated with high-dose cytarabine, an acute demyelinating neuropathy is seen which resembles Guillain-Barre in its clinical symptoms and signs frequently requiring transient respiratory support.

Myopathy

Myopathy is seen in the majority of leukemic patients after several weeks (>3 weeks) of therapy though in susceptible individuals (elderly, deconditioned or malnourished) may appear within days of steroid therapy^{4,12}. The myopathy is proximal, characterized histologically by bland atrophy of type 2 (fast twitch) fibers and preferentially affects the lower extremities however over time shoulder weakness is also seen. Therapy entails steroid reduction and if possible discontinuance. Recovery after steroid taper not infrequently requires months before power returns to normal.

Conclusions

Leukemia is associated with a myriad of neurological complications (Table 1) that occur both as a direct consequence of leukemia (leukemic meningitis, chloroma) and indirectly due treatment or immunosuppression. Most relevant with respect to differential diagnosis however is leukemic meningitis. LM by affecting the entire CNS may present in a pleomorphic manner and mimic a variety of neurologic syndromes. Therefore in essentially all leukemic patients with CNS dysfunction, a CSF examination is necessary. By contrast, peripheral nervous system disorders are nearly always treatment related (steroid myopathy, vinca alkaloid neuropathy) and respond best to discontinuance of the neurotoxic agent.

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Table 1: Neurologic Complications of Leukemia

- Direct
 - Meningeal
 - ❖ Leukemic
 - Parenchymal
 - ❖ Tumor
 - ❖ Hemorrhage
 - Vascular slugging/stasis due to hyperleukocytosis
 - Thrombocytopenia due to leukemia or treatment
 - Epidural
 - ❖ Leukemic
- Indirect
 - Meningeal
 - ❖ Infectious
 - Bacterial meningitis
 - Fungal meningitis
 - Chemical meningitis
 - ❖ Headache
 - Low-pressure headache (post-lumbar puncture)
 - Subdural hematoma
 - Parenchymal
 - ❖ Hemorrhage
 - Treatment-induced sinus thrombosis (l-asparaginase)
 - Treatment-induced thrombocytopenia
 - Moyamoya disease
 - Disseminated intravascular coagulation
 - Fungal-related
 - Mycotic aneurysm
 - Vasculitis
 - ❖ Encephalopathy
 - Radiation-related
 - Methotrexate related
 - Toxic-metabolic
 - Organ failure
 - Spinal
 - ❖ Treatment-related (intra-thecal drugs) myelopathy
 - Epidural
 - ❖ Hemorrhage
 - Treatment-induced thrombocytopenia
 - ❖ Steroid-related epidural lipomatosis
 - Peripheral neuropathy
 - ❖ Treatment-related (vinca alkaloids)
 - Myopathy
 - ❖ Treatment-related (corticosteroids)

Table 2: Intra-CSF Chemotherapy for Neoplastic Meningitis

Drugs	Induction Regimens		Consolidation Regimen		Maintenance regimen	
	Bolus Regimen	CxT Regimen	Bolus Regimen	CxT Regimen	Bolus Regimen	CxT Regimen
Methotrexate	10-15mg twice weekly (Total 4 weeks)	2mg/day for 5 days every other week (Total 8 weeks)	10-15mg once weekly (total 4 weeks)	2mg/day for 5 days every other week (total 4 weeks)	10-15mg once a month	2mg/day for 5 days once a month
Cytarabine	25-100mg 2 or 3 times weekly (Total 4 weeks)	25mg/day for 3 days weekly (Total 4 weeks)	25-100mg once weekly (Total 4 weeks)	25mg/day for 3 days every other week (Total 4 weeks)	25-100mg once a month	25mg/day for 3 days once a month
DepoCyt®	50mg every 2 weeks (Total 8 weeks)		50mg every 4 weeks (Total 24 weeks)			
Thiotepa	10mg 2 or 3 times weekly (Total 4 weeks)	10mg/day for 3 days weekly (total 4 weeks)	10mg once weekly (Total 4 weeks)	10mg/day for 3 days every other week (Total 4 weeks)	10mg once a month	10mg/day for 3 days once a month
α-Interferon	1x10 ⁶ u 3 times weekly (Total 4 weeks)		1x10 ⁶ u 3 times weekly every other week (Total 4 weeks)		1x10 ⁶ u 3 times weekly one week per month)	