Central Nervous System Involvement in Adult Acute Lymphocytic Leukemia

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21.1 Introduction

Central nervous system (CNS) involvement is identified at the time of diagnosis in less than 5% of children with acute lymphoblastic leukemia (ALL) [1]. However, prior to the institution of adequate CNS prophylaxis, it was a major obstacle to cure in childhood ALL as 50–75% of patients would eventually relapse in the CNS [1, 2]. The routine use of CNS prophylaxis has improved the long-term prognosis of patients, and CNS relapse occurs in less than 10% of patients treated with contemporary protocols [3]. Effective means of CNS prophylaxis include cranial irradiation, intrathecal chemotherapy (IT), and high-dose systemic chemotherapy (HDCT) with agents that can cross the blood-brain barrier [4]. A risk-oriented approach has been developed for childhood CNS prophylaxis, in an attempt to reduce the occurrence of CNS relapse while minimizing the potentially serious adverse effects of radiotherapy and chemotherapy [4].

Less than 10% of adults with ALL have CNS involvement at presentation [5, 6]. However, without CNS prophylaxis, approximately one third of patients will eventually have CNS involvement [6–8], with a 5-year CNS event-free survival rate of 42% [5]. These data may be an underestimation as CNS disease has been identified at autopsy in patients who were thought to have bone marrow disease only [9]. CNS prophylaxis in adults has mostly been patterned after studies in childhood ALL, but several features are unique to adult ALL. Unfortunately, few studies dealing with CNS leukemia in adult ALL have been reported. Herein we review some of the relevant aspects of CNS disease in adult ALL including diagnostic and prognostic criteria, current prophylaxis and treatment options.

21.2 Diagnosis

Cytologic examination of the CSF is the most important tool for the diagnosis of meningeal localization of lymphoid malignancies. However, early meningeal involvement may be difficult to detect and false-negative rates up to 40% for the first lumbar puncture have been reported [10]. Patients with leukemia often develop CSF lymphocytosis. Staining for terminal deoxynucleotidyl transferase (TdT) is helpful to distinguish between leukemic lymphoblasts and normal lymphocytes [11, 12]. However, unequivocal identification of leukemic cells
in nontraumatic lumbar puncture in the CSF, regardless of cell count, signifies clinical meningeal leukemia.

CNS involvement among children with ALL has historically been defined at most institutions by either the presence of at least 5 leukocytes per microliter of cerebrospinal fluid (CSF) associated with the presence of leukemic blasts (identified on a cytocentrifuged preparation) or the presence of a cranial nerve palsy on physical examination [13]. A large trial conducted at St. Jude's Hospital introduced a new classification of patients with ALL and CNS status at diagnosis: CNS1 denotes the absence of identifiable leukemic blast cells in CSF; CNS2, the presence of blast in a sample that contains <5 WBC/μl; and CNS3, a nontraumatic sample that contains ≥5 WBCs/μl with identifiable blasts, or the presence of a cerebral mass or cranial nerve palsy with leukemic cells in CSF [14]. The probability of 5-year CNS leukemia-free survival for CNS1 was significantly higher than for CNS2 and CNS3 (96% vs. 87% vs. 74% respectively) (p<0.001). The projected 5-year survival rates for these groups of patients were 75%, 49%, and 53% respectively [14].

Although the adverse prognosis of CNS2 status was confirmed by the Pediatric Oncology Group [15] several other investigators could not confirm this association among patients classified as having intermediate-risk ALL [16–18]. This discrepancy can be explained by differences in treatment regimens and in the clinical characteristics of the patients studied.

It has been argued that leukemic blasts may be iatrogenically introduced into the cerebrospinal fluid by a traumatic lumbar puncture (defined as more than 10 red blood cells per μl of CSF). A recent report by Gajjar et al. [19] provides evidence of the adverse impact of a traumatic lumbar puncture at the time of diagnosis on treatment outcome of children with ALL. The EFS for patients with one CSF sample contaminated with blasts was worse that that for patients with no contaminated CSF (5-year EFS estimates 76±6% and 60±6% respectively, p = 0.026); for those patients with two consecutive contaminated CSF the 5-year EFS was 46±9%. In a Cox multiple regression analysis, the strongest prognostic indicator was two consecutive contaminated CSF samples, with a hazard ratio of 2.39 [95% confidence interval (CI) 1.36–4.20]. Investigators from Germany published a large retrospective study among 2,021 pediatric patients with ALL, enrolled in the BMF-95 trial [18]. Patients were analyzed according to type of CNS involvement and traumatic lumbar puncture (TLP) with (+) or without (−) CNS blasts. CNS2, CNS3, and TLP+ groups contained a higher percentage of patients with unfavorable characteristics. Cox regression analysis identified TLP+ and CNS3 status as prognostically significant. The CNS3 risk ratio was 2.3 with 95% CI, 1.4 to 3.6, p = 0.0005; the TLP+ risk ratio was 1.5 with 95% CI, 1.02 to 2.2; p = 0.04. Five-year event-free survival (EFS) was 79% overall, 80% for CNS1, and 83% for TLP−. CNS2 patients have an EFS of 80%, but the cumulative incidence of relapses with CNS involvement is higher compared with CNS1 patients (0.10 vs. 0.04). TLP+ patients have a significantly reduced EFS (73%, p = 0.003) because of an increased incidence of CNS relapses. CNS3 patients suffer from more systemic and CNS relapses (EFS 50%) (Fig. 21.1). These data emphasize the importance of a properly performed lumbar puncture by an experienced clinician particularly at diagnosis, when higher numbers of blast cells are circulating in the peripheral blood [20].

There has been no organized analysis of these or other criteria for adult ALL. Currently, CNS leukemia is defined by the presence of >5 WBC/μl in the CSF, with morphologically unequivocal lymphoblasts in cytocentrifuged sample [21]. However, the presence of blasts in the CSF when the WBC is <5/μl may have a similar clinical significance [14].

Several markers of CNS disease have been investigated to substitute or complement the results of cytology. DNA content may be abnormal and has a high