



ORIGINAL ARTICLE

Association between traumatic lumbar puncture and the risk of central nervous system relapse in adults with acute lymphoblastic leukaemia



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KEYWORDS

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Abstract Intrathecal chemoprophylaxis prevents central nervous system relapses in patients with acute lymphoblastic leukaemia (ALL) but few studies have addressed the predictive markers of relapse. Among these, traumatic lumbar puncture (TLP) has been associated with lower disease-free survival (DFS).

To investigate the risk posed by TLP on relapse and DFS, we assembled a retrospective cohort including 79 patients with ALL who received intrathecal chemoprophylaxis during 2009 to 2013. One TLP per patient was recorded in 49 cases, and more than one TLP in 3. Mean follow-up was 283 (22–1118) days with an overall DFS of 68%. DFS was significantly lower in the group that had experienced TLP (58% vs 100% [$P = .070$]). Multiple TLP posed a greater risk of relapse than single TLP ($P = .001$). In conclusion, TLP in adults constitutes a major risk factor, greater than that reported in the large paediatric series.

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PALABRAS CLAVE

Punción espinal;
Supervivencia sin
enfermedad;

Asociación entre punción lumbar traumática y riesgo de recaída al sistema nervioso central en adultos con leucemia linfoblástica aguda

Resumen La quimioprofilaxis intratecal evita la recaída a sistema nervioso central en pacientes con leucemia linfoblástica aguda (LAL), aunque poco se ha estudiado sobre

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marcadores predictivos de recaída. Entre estos, la punción lumbar traumática (TLP) se ha asociado con una menor supervivencia libre de la enfermedad (EFS).

Para investigar el riesgo que infiere la TLP sobre la recaída y la EFS, se formó una cohorte retrospectiva compuesta por 79 pacientes con LAL que recibieron quimioprofilaxis intratecal durante 2009 a 2013. Se registró una TLP por paciente en 49 casos y más de una en 3. La media de seguimiento fueron 283 (22–1118) días, con EFS global del 68%, significativamente menor en quienes recibieron alguna TLP (58% vs 100% [$p=0.070$]). Múltiples TLP aportaron mayor riesgo que TLP única ($p=0.001$). En conclusión, las TLP en adultos son un factor de riesgo preponderante, con mayor relevancia de lo reportado en las grandes series pediátricas.

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Introduction

At present acute lymphoblastic leukaemia with B or T precursors is treated using block sequential chemotherapy regimens in conjunction with immunotherapy and tyrosine kinase inhibitors, and unlike other leukaemias, it requires prophylaxis therapy due to the high risk of central nervous system relapse.^{1–4} In its infancy, prophylaxis consisted of radiation therapy to the head followed by high doses of methotrexate plus intrathecal chemotherapy. Most of our knowledge on prophylaxis and relapse has been gained from paediatric protocols. Conter and collaborators in the AIEOP group substituted chemotherapy for a regime of high doses of intrathecal methotrexate (5 g/m² for four courses) and achieved a relapse-free survival of above 90%, recording a recurrence rate of only 5%.⁵ This strategy has been validated by other authors around the world with similar relapse rates,^{6,7} and therefore intrathecal chemotherapy became the standard prophylaxis therapy for the central nervous system (CNS), the triple combination strategy being the most popular.⁸ There are few studies in adults in this regard, and most of them agree that adequate prophylaxis prevents CNS relapse.⁹ There are also few predictive markers of relapse. Sancho and collaborators only managed to identify lactate-dehydrogenase as a predictive marker of relapse.¹⁰ Traumatic lumbar puncture as a CNS relapse risk is another factor of interest. In general, most series agree that the presence of traumatic cerebrospinal fluid with blasts shortens relapse-free survival and that CNS1 and CNS2 liquids behave similarly.^{11,12} In our hospital, triple-drug therapy (cytarabine, methotrexate and hydrocortisone) has been effective in controlling isolated CNS relapses.¹³ This is because our institutional protocol uses intensive doses of intrathecal chemotherapy, and the objective proposed was to establish whether there is an association between traumatic lumbar puncture and the risk of CNS relapse.

Patients and methods

Protocol design

An observational study based on a retrospective cohort of patients with de novo acute lymphoblastic leukaemia treated in the haematology department of the General

Hospital of Mexico between December 2009 and July 2013. These patients had received first-line treatment and prophylaxis directed at the central nervous system using intrathecal chemotherapy. Patients who were to receive radiotherapy or who did not have basal cerebrospinal fluid for analysis were excluded from the study.

Treatment

Institutional protocol HGMLAL07 has been available in our hospital from 2007 to the present date as first-line treatment for patients with adult acute lymphoblastic leukaemia. This protocol includes a pre-induction phase with steroids similar to protocol GIMEMA ALL0087 and intensification phases during the maintenance phase. Central nervous system-directed prophylaxis was given in four doses of intrathecal chemotherapy during the induction of remission phase, followed by monthly doses during the six consolidation blocks and then bimonthly doses over the 2 years of maintenance. The chemotherapy regimen included 15 mg methotrexate, 40 mg cytarabine and 8 mg dexamethasone. The patients who were treated with the Hyper-CVAD regimen received chemotherapy on days 2 and 8 of each course with 15 mg methotrexate and 100 mg cytarabine respectively.

The cerebrospinal fluid was examined by cytopspin (ROTOFIX 32 A, ZENTRIFUGEN brand at 6000 rpm), it was then stained with Wright–Giemsa and examined at increases of 10 \times and 100 \times .

The status for considering central nervous system infiltration was based on the following criteria: CNS1, non-traumatic lumbar puncture (<10 erythrocytes/ μ L); CNS2, non-traumatic lumbar puncture with a white blood cell count of less than 5 μ L and blasts in the cerebrospinal fluid; CNS3, non-traumatic lumbar puncture with >5 white blood cells and blasts in the CSF. For the statistical analysis, it was considered traumatic fluid (TLP) if it had >10 erythrocytes/ μ L and lumbar puncture with infiltration if blasts were present in the cerebrospinal fluid.

Statistical analysis

Central nervous system relapse-free survival was considered from the date of diagnosis until the date of relapse, death or the last date recorded on the medical record.

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