Methotrexate, can we do without it?

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Medications such as penicillin, chloramphenicol, and tetracycline emerged during the 1940s. In December 1947, Sydney Farber, a Jewish physician, a pediatric pathologist at the Children’s Hospital of Boston administered it, for the first time, for the treatment of a child with acute lymphoblastic leukemia (ALL) a new compound, an antifolate agent called aminopterin or methotrexate (MTX), this was provided to Farber by a long-time friend of his Yella Subbaro, a Hindu doctor who was working at the Lederle Laboratories in New York at the time, he had discovered it while he tried to synthesize folic acid, vitamin whose deficiency explained megaloblastic anemia, a very common pathology at that time.

At varying doses, by different routes of administration, at various stages of each of the diseases and applied alone or in combination with other medications, the following are some of the current indications of MTX: rheumatoid arthritis, psoriasis, atopic dermatitis, Crohn’s disease, ectopic pregnancy, head and neck tumors, trophoblastic and choriocarcinoma tumors, breast, lung, and bladder neoplasms, fungoid mycosis, osteosarcoma, Langerhans cell histiocytosis, Hodgkin’s lymphoma, various unicellular lymphomas, graft versus host disease, acute myeloblastic leukemia, and ALL.

Next, some aspects of the value of MTX, specifically in the treatment of ALL will be discussed. This is the most common neoplasm in the pediatric age, and it is practically suffered by one in three children with cancer. Fortunately, it is also one of the neoplasms in which the highest cure rates have been obtained, currently over 75%. Although different chemotherapy protocols are used for their management (total therapy of St. Jude Hospital and the Berlin, Frankfurt, Munster protocol from the German group, to mention the two most important and used). Most of them divide the treatment of ALL in different phases; induction to remission, consolidation and/or intensification, maintenance of remission, and prophylaxis to prevent infiltration by ALL of the central nervous system (CNS), except for induction, MTX is used in all other phases of treatment.

The cases of ALL are divided according to the risk of a relapse to occur in three or four categories, those patients with a high risk of relapse receive more intensive treatment. In our country, as in most of the non-first world countries, most of the cases that are treated belong to this risk group. In part, this can be explained by the delay in their diagnosis. During the intensification phase, high doses of MTX are administered, which ranges between 1 and 5 g/m² of body surface, usually in a continuous infusion for 24 h, and generally in four cycles applied every 2 weeks. The value of this treatment scheme has been proven by different groups for many years, although other medications such as cytarabine can be used at high doses, in no way can it replace MTX.

In the prophylaxis phase so that leukemia cells are not present in the CNS, it always includes the administration of intrathecal (IT) chemotherapy of a combination of two...
or three medications, cytarabine, corticosteroids, and MTX. Of these three drugs mentioned, MTX is the only one that cannot be omitted. The first dose of IT chemotherapy is usually applied in the 1st week after diagnosis, and from there on, it is continued to be administered periodically during the first 12 or 18 months. If despite the prophylactic administration of the IT chemotherapy, the patient develops CNS involvement, the applications of IT chemotherapy are intensified and administered together with the high doses of MTX already mentioned.

The last phase of the treatment of children with ALL is known as the remission maintenance phase; here, two medications are administered orally, mercaptopurine daily and MTX on a weekly basis, both are started at the end of the intensification phase and continued until the end of treatment, between 24 and 30 months; during this phase, the objective is for the patient to maintain leukocyte counts between 3000 and 4000 per mm³. Although the highest and fastest destruction of leukemic cells occurs at the beginning of treatment, especially in the induction phase, it is the combination of mercaptopurine and MTX as important as the intense initial treatment. There is no way to modify this therapy without having a negative impact on the final result.

Therefore, it can be concluded that at least in the treatment of ALL, the most common cancer in children, MTX cannot be substituted or omitted; not using it would have a very negative effect and would make the cure of a patient very unlikely of a disease that can currently be resolved in more than 70% of pediatric patients.

Conflicts of interest

The authors declare that they have no conflicts of interest.