ABSTRACT

Retinoids are lipophilic compounds derived from vitamin A, which have been extensively studied in cancer prevention and therapy. In pediatric oncology, they are successfully used for the treatment of acute promyelocytic leukemia (APL) and high-risk neuroblastoma (HR-NBL). APL is a subtype of acute myeloid leukemia (AML) clinically characterized by a severe bleeding tendency with a high-risk of fatal hemorrhage. The molecular hallmark of this disease is the presence of the promyelocytic leukemia (PML)-retinoic acid receptor-α (RAR α) gene fusion that plays a critical role in promyelocytic leukemogenesis and represents the target of retinoid therapy. The introduction in the late 1980s of all-trans retinoic acid (ATRA) into the therapy of APL radically changed the management and the outcome of this disease. Presently, the standard front-line therapeutic approach for pediatric APL includes anthracycline-based chemotherapy and ATRA, leading to a complete remission in almost 90% of the patients. Neuroblastoma (NBL) is an aggressive childhood tumor derived from the peripheral neural crest. More than half of patients have a high-risk disease, with a poor outcome despite intensive multimodal treatment. Although the exact mechanism of action remains unclear, the introduction of 13-cis-retinoic acid (13-cis-RA) in the therapy of NBL has improved the prognosis of this disease. Currently, the standard treatment for HR-NBL consists of myeloablative therapy followed by autologous hematopoietic stem cell transplantation (HSCT) and maintenance with 13-cis-RA for the treatment of minimal residual disease, leading to a 3-year disease-free survival rate (DFS) of about 50%. In this paper the authors provide a review of the peer-reviewed literature on the role of retinoids in the treatment of pediatric APL and HR-NBL, summarizing the
most relevant clinical trial results of the last decades, analyzing the ongoing trials, and investigating future therapeutic perspectives of children affected by these diseases.

Keywords: 13-Cis-retinoic acid; All-trans retinoic acid; Clinical trials; Neuroblastoma; Pediatric acute promyelocytic leukemia

INTRODUCTION

Retinoids are lipophilic compounds derived from vitamin A, including 13-cis-retinoic acid (13-cis-RA), all-trans retinoic acid (ATRA), and N-(4-hydroxyphenyl)retinamide (4-HPR). In the last few decades they have been widely studied in cancer prevention and therapy because of their ability to induce differentiation of tumor cells into mature cells [1, 2]. In pediatric onco-hematology, retinoids are successfully used for the treatment of acute promyelocytic leukemia (APL) and high-risk neuroblastoma (HR-NBL) [3].

APL

APL is a subtype of acute myeloid leukemia (AML) characterized by the proliferation of leukemic cells blocked at the promyelocytic stage of myelopoiesis [4, 5]. Severe coagulation disorders, which expose patients to high-risk of fatal hemorrhage, are the clinical hallmark of APL [6].

Molecularly, genomic translocation and the consequent fusion gene promyelocytic leukemia (PML)-retinoic acid receptor-α (RAR-α) is found in almost 95% of APL cases [7, 8]. According to the classical pathophysiological model of APL, the PML-RAR-α fusion protein promotes the accumulation of undifferentiated leukemic cells through the induction of histone deacetylase activity and the inhibition of transcription of RAR-α target genes. In this context, ATRA converts PML-RAR-α into an activator of transcription and restores cell differentiation [3, 9].

The recent findings that PML-RAR-α protein acts on several key pathways involved in leukemogenesis, such as differentiation, self-renewal of myeloid progenitors, and resistance to apoptosis, has suggested a more complex pathogenesis of APL and a different mechanism of action of ATRA. Indeed, according to this hypothesis, ATRA prompts the degradation of aberrant PML-RAR-α protein and restores PML nuclear bodies that are PML domains through which PML performs several functions necessary for normal cell development [10].

The advent of ATRA in the late 1980s has led to a revolution in the prognosis of this disease. Its association with anthracycline-based chemotherapy has increased complete remission (CR) and disease-free survival rate (DFS) of pediatric patients with APL from 70% to 90–95% and from 40% to 80%, respectively [11–13].

NBL

Retinoids have also been widely investigated in solid tumors, especially NBL [14]. Indeed, the in-vivo ability of NBL to spontaneously regress or mature into a differentiated ganglioneuroma encouraged physicians to investigate whether some agents could modify the phenotype of cancer cells in vitro, even leading to morphologically normal cells. Both ATRA and 13-cis-RA induced growth arrest and morphological differentiation of NBL cell lines [14]; however, 13-cis-RA showed a better pharmacokinetic profile with higher peak levels and longer half-life, consistent with better activity against NBL [15, 16].

Approximately 60% of patients diagnosed with NBL have HR-NBL defined by stage 4 disease in children over 1 year of age, stage 3