BBA Clinical 1 (2014) 59–77

Contents lists available at ScienceDirect

BBA Clinical

journal homepage: http://www.journals.elsevier.com/bba-clinical/

Review

Molecular profiling of childhood cancer: Biomarkers and novel therapies

Federica Saletta [a], Carol Wadham [b], David S. Ziegler [b,c], Glenn M. Marshall [b,c], Michelle Haber [b], Geoffrey McCowage [d], Murray D. Norris [b], Jennifer A. Byrne [a,e,*]

[a] Children's Cancer Research Unit, Kids Research Institute, Westmead 2145, New South Wales, Australia
[b] Children's Cancer Institute Australia, Lowy Cancer Research Centre, UNSW, Randwick 2031, New South Wales, Australia
[c] Kids Cancer Centre, Sydney Children's Hospital, Randwick 2031, New South Wales, Australia
[d] The Children's Hospital at Westmead, Westmead 2145, New South Wales, Australia
[e] The University of Sydney Discipline of Paediatrics and Child Health, The Children's Hospital at Westmead, Westmead 2145, New South Wales, Australia

ARTICLE INFO

Article history:
Received 20 December 2013
Received in revised form 16 June 2014
Accepted 24 June 2014
Available online 28 June 2014

Keywords:
Childhood cancer
Molecular diagnostics
Targeted therapy
Biomarkers

ABSTRACT

Background: Technological advances including high-throughput sequencing have identified numerous tumor-specific genetic changes in pediatric and adolescent cancers that can be exploited as targets for novel therapies.
Scope of review: This review provides a detailed overview of recent advances in the application of target-specific therapies for childhood cancers, either as single agents or in combination with other therapies. The review summarizes preclinical evidence on which clinical trials are based, early phase clinical trial results, and the incorporation of predictive biomarkers into clinical practice, according to cancer type.
Major conclusions: There is growing evidence that molecularly targeted therapies can valuably add to the arsenal available for treating childhood cancers, particularly when used in combination with other therapies. Nonetheless the introduction of molecularly targeted agents into practice remains challenging, due to the use of unselected populations in some clinical trials, inadequate methods to evaluate efficacy, and the need for improved preclinical models to both evaluate dosing and safety of combination therapies.
General significance: The increasing recognition of the heterogeneity of molecular causes of cancer favors the continued development of molecularly targeted agents, and their transfer to pediatric and adolescent populations.

Contents

Abbreviations: ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ARMS, alveolar rhabdomyosarcoma; AT/RT, atypical teratoid/rhabdoid tumor; AURKA, aurora kinase A; AURKB, aurora kinase B; BET, bromodomain and extra terminal; CAR, chimeric antigen receptor; CML, chronic myeloid leukemia; DFMO, difluoromethylornithine; DIPG, diffuse intrinsic pontine glioma; EGFR, epidermal growth factor receptor; ERMS, embryonal rhabdomyosarcoma; HDAC, histone deacetylases; Hsp90, heat shock protein 90; IGF/IGFR, insulin-like growth factor/receptor; IGF-1R, insulin-like growth factor type 1 receptor; mAb, monoclonal antibody; mAbs, monoclonal antibodies; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; ODC1, ornithine decarboxylase 1; PARP, poly(ADP-ribose) polymerase; PDGFRA/B, platelet derived growth factor alpha/beta; Ph+, Philadelphia chromosome-positive; PI3K, phosphatidylinositol 3′-kinase; PLK1, polo-like kinase 1; RMS, rhabdomyosarcoma; SHH, sonic hedgehog; SMO, smoothened; SYK, spleen tyrosine kinase; TOP1/TOP2, DNA topoisomerase 1/2; TRAIL, TNF-related apoptosis-inducing ligand; VEGF/VEGFR, vascular endothelial growth factor/receptor

* Corresponding author at: Children's Cancer Research Unit, Kids Research Institute, The Children's Hospital at Westmead, Locked Bag 4001, Westmead 2145, New South Wales, Australia. Tel.: +61 2 9845 3027, fax: +61 2 9845 3078.
E-mail address: jennifer.byrne@health.nsw.gov.au (J.A. Byrne).

http://dx.doi.org/10.1016/j.bbacli.2014.06.003

1. Introduction

Childhood cancers are rare, representing less than 1% of new cancer diagnoses, however, they are still the leading cause of disease-related death in children in industrialized countries such as the US [1]. Children's malignancies are generally treated with a combination of cytotoxic chemotherapy, radiation, surgery, and occasionally bone marrow transplant, which have markedly improved the overall 5-year survival rate over the past decades from 50 to 60% for cases diagnosed during the 1970s, to over 80% today [2].

The greatest contribution to better outcomes comes from advances in our understanding of the genetics of cancer [3–5], and the discovery of molecular biomarkers and incorporation of novel targeted agents has led to improved outcomes for cancer patients, and decreases in both short- and long-term toxicities [6]. Some biomarkers are routinely used for diagnostics (such as Ki-67 staining as proliferation index) [7], risk-stratification (*MYCN* amplification in neuroblastoma) [8] and monitoring (S100-beta in melanoma) [9]. Others are used to direct the use of targeted therapy, such as the fusion tyrosine–kinase protein BCR–ABL for the use of imatinib in chronic myeloid leukemia (CML) and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) [10,11] or *anaplastic lymphoma kinase* (*ALK*) mutations (especially EML4–ALK rearranged cancers) for the use of crizotinib, the ALK inhibitor approved for treatment of non-small cell lung cancer (NSCLC) [12,13]. In summary, the genetic heterogeneity now recognized to underpin pediatric and adolescent cancers may be exploited by agents targeting these specific molecular/genetic lesions. A principal challenge is to now further expand the number of molecular targets investigated, and integrate conventional practices with the best target-matched therapies. The aim of this review is to give an overview of recent advances in the application of "druggable" biomarkers, and the use of target-specific therapies for childhood cancers.

2. Relevant biomarkers in childhood malignancies and novel therapies

The role of germ-line mutations in explaining susceptibility to childhood cancer and genetic predisposition to familial malignancies is well established [14], whereas the roles of somatic, acquired mutations have become a central subject of study in more recent years. Cancer biomarkers are now increasingly used to characterize human tumors and to explain the heterogeneity that exists between different tumors. Such heterogeneity is reflected by the wide range of sub-classifications (diagnostic markers) and risk-stratifications (prognostic markers) existing for many cancer types, as well as by the increasing number of molecules able to forecast the response of patients to personalized therapies (predictive markers) [15].

The following sections represent an overview of relevant markers and matched therapies in pediatric tumors. A full list of the molecular inhibitors reviewed is available in Table 1, while a schematic summary of cancer pathway inhibition is shown in Fig. 1. Table 2 reports the frequency of mutation/overexpression of some biomarkers relevant in childhood cancer.

2.1. Leukemias

Leukemias are the most common type of childhood cancers, accounting for one-third of all cancers diagnosed in children. Among them, ALL accounts for approximately three-quarters of all childhood leukemia diagnoses, while acute myelogenous leukemia (AML) is 5 times less frequent. Chronic myeloid leukemia (CML) and chronic lymphocytic leukemia are very rare in the pediatric population [16]. Several chromosomal abnormalities have been identified in pediatric leukemias, including translocations such as t(9;22) BCR–ABL, t(12;21) TEL–AML1, t(8;21) AML1–ETO and t(15;17) PML–RARA [17].