ELSEVIER

Critical Reviews in Oncology/Hematology 83 (2012) 293–302

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Anaplastic large cell lymphoma, ALK-positive

Andrés J.M. Ferreri [a,b,*], Silvia Govi [a,b], Stefano A. Pileri [c], Kerry J. Savage [d]

[a] *Unit of Lymphoid Malignancies, San Raffaele Scientific Institute, Milan, Italy*
[b] *Medical Oncology Unit, Department of Oncology, San Raffaele Scientific Institute, Milan, Italy*
[c] *Haematopathology Unit, Department of Haematology and Oncological Sciences "L. and A. Seràgnoli", Bologna University School of Medicine, Bologna, Italy*
[d] *Division of Medical Oncology, British Columbia Cancer Agency, Vancouver, Canada*

Accepted 14 February 2012

Contents

1. General information 294
   1.1. Definition 294
   1.2. Incidence and risk factors 294
   1.3. Anaplastic lymphoma kinase (ALK) 294
2. Pathology and biology 295
   2.1. Morphology 295
   2.2. Immunophenotype 295
   2.3. Genetic features 295
3. Diagnosis 296
   3.1. Clinical presentations 296
4. Staging system and procedures 296
5. Prognosis 296
6. Treatment 297
   6.1. First-line treatment 297
   6.2. Treatment of relapsed or refractory disease 298
   6.3. New drugs or experimental approaches 298
   Conflict of interest statement 299
   Reviewer 299
   References 300
   Biographies 302

Abstract

Anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-positive (ALK+ ALCL) is an aggressive CD30-positive T-cell lymphoma that exhibits a chromosomal translocation involving the *ALK* gene and the expression of ALK protein. No particular risk factor has been clearly identified for ALCL. ALK+ ALCL shows a broad morphologic spectrum, but all cases contain a variable proportion of cells with eccentric, horseshoe- or kidney-shaped nuclei often with an eosinophilic region near the nucleus (hallmark cells). Five morphologic patterns can be recognized. ALK+ ALCL occurs in young subjects (median age ~35 years), with male predominance, and frequently presents at an advanced stage, with systemic symptoms and extranodal involvement. Near 40% of patients are low risk according to the International Prognostic Index (IPI). Overall, the prognosis of ALK+ ALCL is remarkably better than other T-cell lymphomas. The IPI and the PIT scores in general predict survival in patients with ALK+ ALCL. Standard first-line treatment for ALK+ ALCL consists of doxorubicin-containing

* Corresponding author at: Unit of Lymphoid Malignancies, Medical Oncology Unit, Department of Oncology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy. Tel.: +39 02 26437649; fax: +39 02 26437625.
E-mail address: andres.ferreri@hsr.it (A.J.M. Ferreri).

1040-8428/$ – see front matter
doi:10.1016/j.critrevonc.2012.02.005

polychemotherapy, which is associated with an overall response rate of ∼90%, a 5-year relapse-free survival of ∼60%, and a 5-year overall survival of 70%. Excellent results have been reported with a variety of anthracycline-based chemotherapy regimens including CHOP, CHOEP or MACOP-B. Consolidative high-dose chemotherapy and autologous stem cell transplantation (HDC/ASCT) has also been evaluated in patients in first remission with favourable results, however, superiority to standard chemotherapy is unproven and this approach remains investigational. Following universally accepted guidelines for the treatment of failed aggressive lymphomas, HDC/ASCT can effectively salvage a proportion of patients with relapsed or refractory ALK+ ALCL. Recently, the development of novel therapies targeting CD30 and ALK appear promising.

Keywords: Anaplastic lymphoma; CD30; *ALK*; ALK inhibitors; Autologous transplant; Allogeneic transplant

1. General information

1.1. Definition

Anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-positive (ALK+ ALCL) was first described by Stein et al. in 1982 [1]. It is a peripheral T-cell lymphoma (PTCL) consisting usually of large neoplastic cells with abundant cytoplasm and pleomorphic, often horseshoe-shaped, nuclei, with a translocation involving the *ALK* gene, and expression of ALK protein, as well as of CD30. ALCL with similar morphologic and phenotypic features, but lacking the *ALK* rearrangement and the ALK protein, are considered as a separate category (ALK-negative (ALK-) ALCL) ALK+ ALCL must be distinguished from primary cutaneous ALCL which is usually ALK- and other subtypes of T- or B-cell lymphoma with anaplastic features and/or CD30 expression. Of note, ALK+ ALCL with a B-cell phenotype is considered a subtype of diffuse large B-cell lymphoma (DLBCL) [2].

1.2. Incidence and risk factors

ALK+ ALCL accounts for about 3% of adult non-Hodgkin lymphomas (NHL) and 10–15% of childhood lymphomas. No particular risk factors have been clearly identified for ALCL. Presently, there is no convincing evidence that viruses causing NHL in humans, such as Epstein–Barr virus, human T-cell leukaemia/lymphoma virus family, or others are involved in the origin of ALCL. The pathogenetic implication of the t(2;5) chromosomal translocation and NPM (nucleophosmin)-ALK fusion product are matter of study. ALK, a receptor tyrosine kinase (RTK) in the insulin receptor superfamily, was originally identified as the oncogenic NPM-ALK fusion protein due to a t(2;5) in ALCL. Many other chromosomal rearrangements or gene mutations/amplification leading to enhanced ALK activity have subsequently been identified and characterized in a number of human cancer types (see below). No particular correlation between ALCL and inherited immunological deficiency disease, or other immunological disorders has been reported. There are no convincing data concerning the role of chronic antigenic stimulation in the genesis of ALCL. Several chemical substances such as solvents, pesticides and fertilizers, as well as dusts and particles, hair dye, smoking and diet have been suggested as possible aetiological factors in NHL [2]. Although specific studies have not been undertaken in ALCL patients, all histotypes of NHL have been described as occurring in people whose work involves application of solvents, pesticides and fertilizers [3–6].

T-cell lymphomas represent 3% of the lymphomas related to HIV infection [7]. Some reported T-cell lymphomas were actually CD30+ B-cell lymphomas with down-regulation of B-cell antigens due to Epstein–Barr virus-coinfection [8] or PTCL with large cells [9]. ALCL is not included among WHO-classification of HIV-correlated lymphomas, but at least 20 cases have been reported, with rare cases of ALK expression [10]. HIV-related ALCLs were characterized by poor prognosis, rapid clinical deterioration, nosocomial infections, and diagnostic delay [11].

1.3. Anaplastic lymphoma kinase (ALK)

ALK is an orphan receptor tyrosine kinase first identified as part of the t(2;5) associated with most ALCL and a subset of T-cell [12] ALK signalling can be activated by the establishment of unique oncogenic fusions of the ALK gene at chromosomal band 2p23 with a variety of partners through chromosomal translocation events [12], resulting in the generation of oncogenic ALK fusion genes and their encoded proteins. ALK is one of the few oncogenes activated in both haematopoietic and non-haematopoietic malignancies. Approximately 70–80% of ALK+ ALCL express the NPM-ALK fusion protein derived from the t(2;5)(p23;q35), and about the same frequency of ALCLs stain positive for ALK by immunohistochemistry (see below) [13,14]. These oncogenic fusion proteins and ALK kinase domain activation have been also identified in various solid tumours, like non-small cell lung cancers and neuroblastoma [15,16].

The extracellular region of ALK shows significant homology to the leukocyte tyrosine kinase [19], which places ALK in the insulin receptor superfamily of RTKs. The ALK gene encodes a 1,620-amino acid protein that undergoes post-translational N-linked glycosylation to a fully mature form weighing 220 kDa. ALK expression is restricted to the developing central and peripheral nervous system with a postulated role in participating in the regulation of neuronal differentiation [17]. Although constitutive ALK signalling has