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New Drugs

Cutaneous T-cell lymphomas: Focusing on novel agents in relapsed and refractory disease

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ABSTRACT

Patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL) display a dismal prognosis and their therapy represents an unmet medical need, as the best treatment strategy is yet to be determined. Exciting data on novel targeted agents are now emerging from recently concluded and ongoing clinical trials in patients with relapsed and refractory CTCL. Three FDA approved compounds are used as single agents including the oral retinoid bexarotene and histone deacetylase inhibitors romidepsin and vorinostat. Brentuximab vedotin, an anti-CD30 drug-conjugated monoclonal antibody, has received from European Commission the orphan designation but has not been approved by EMA yet. Several other molecules have demonstrated their activity in the same context and combination strategies are being explored. Participation in a well designed clinical trial is encouraged, as the introduction of novel agents will continue to expand the therapeutics options available in the management of CTCL.

Introduction

Cutaneous T-cell lymphomas (CTCLs) comprise a clinical-pathologically heterogeneous group of uncommon non-Hodgkin lymphomas that manifest primarily in the skin, but also may involve lymph nodes, blood, bone marrow and viscera. CTCLs are generally considered incurable unless allogeneic stem cell transplantation is implemented. CTCL is usually diagnosed in middle to late adulthood and is significantly more common in men than women. Diagnosis of CTCL is often difficult in the early stages because of their slow progression and ability to mimic many other benign skin conditions: e.g. the early patches of CTCL resemble closely the rashes of eczema, psoriasis, and contact dermatitis. As a further complication, the early manifestations of the disease can respond favorably to the topical corticosteroid treatments prescribed for these skin disorders and also to sunlight, in some instances. This has the unfortunate result of the disease being missed and the patient remaining untreated for years.

Many theories exist regarding the causes of CTCL: some evidence suggests that infectious agents, oncogenes, cytokines, occupational or environmental exposures, and viruses are involved. However, the etiology of CTCL, as a whole, is uncertain and, overall, these diseases remain an enigma: solving it is one of the biggest challenges in hematology.

Definitive diagnosis of CTCL is made by correlating the clinical presentation with the results of skin histology and ancillary tests. The European Society for Medical Oncology (ESMO) states that the diagnosis of CTCL should be based on a combination of clinical,

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histological and immunophenotypical data with molecular studies acting as a valuable adjunct in selected cases [1]. On the basis of these findings, and other tests specific to the level of progression of the disease, the clinical stage of the patient is assessed, providing prognostic correlations.

The World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) have reached a consensus on the classification of cutaneous lymphomas. This classification is based primarily on distinct disease entities with predictable treatment responses and prognoses. The most common CTCL subtype is mycosis fungoides (MF) [2], which together with its more aggressive leukemic and erythrodermic variant, Sézary syndrome (SS), accounts for about 65% of all CTCLs [3,4]. Other CTCL subtypes are represented by primary cutaneous CD30+ TCL (primary cutaneous anaplastic large cell lymphoma [pcALCL] and lymphomatoid papulosis [LyP], which represent at least 25% of all CTCLs [5] and rarer entities, such as primary cutaneous gamma/delta type TCL, primary cutaneous CD8+ aggressive epidermotropic TCL, and primary cutaneous CD4+ small/mediumTCL. The aggressiveness of CTCL is variable among entities: MF, primary cutaneous CD30+ TCL (pcALCL/LyP), and primary cutaneous CD4+ small/medium TCL tend to run a rather indolent course, whereas SS and other rare primary cutaneous TCL entities are often associated with rapid progression and low survival rates [6,7]. Five-year survival rates vary from 25 to 40% in SS to 73–100% in MF or primary cutaneous CD30+ TCL (MF 88–91%, LyP 73–100%, and pcALCL 95–96%) [5,8,9].

Because of the chronic and recurrent nature of CTCL, patients frequently require repeated treatment courses and maintenance regimens for disease control. CTCLs are generally treated using a multimodal approach involving hematologists, dermatologists and radiation therapists. Goals of therapy are to control symptoms, maintain cosmesis and improve survival by maximally reducing the tumor burden. Current treatment consists of skin-directed therapy for early stage disease and systemic therapy for advanced stage or refractory early stage disease. Three FDA approved compounds are used as single agents: including the oral retinoid, bexarotene, and histone deacetylase inhibitors (HDAC), romidepsin and vorinostat. Brentuximab vedotin (BV), an anti-CD30 drug-conjugated monoclonal antibody (mAb), has received from European Commission the orphan designation but has not been approved by EMA yet.

Despite the availability of a number of active systemic therapeutic strategies, including biological therapy, cytotoxic chemotherapy and extracorporeal photophoresis, there is an unmet need for targeted therapies, with favorable therapeutic indices, for the treatment of advanced-stage and refractory CTCLs, which often render patients highly susceptible to infection. As treatment of advanced-stage MF/SS is largely palliative, a stage-based approach utilizing sequential therapies in an escalated fashion is preferred. Participation in a well designed clinical trial is encouraged, as the introduction of novel agents will continue to expand the therapeutics options available in the management of CTCLs [10]. At the time of writing, 56 clinical trials result ongoing with open enrollment (clinicaltrial.gov accessed on December 2016).

Purpose of the present paper is to review the mechanisms of action of investigational agents and the clinical results obtained in clinical trials involving CTCL patients (Table 1). Possible newer drug combinations, already being tested in ongoing clinical trials will also be discussed. To this aim, a literature search was conducted to identify studies reporting clinical outcomes following drug therapy in patients with relapsed and/or refractory CTCL (according to WHO and EORTC classification) [6]. MED-LINE (PubMed) was searched for studies published up to December 6, 2016, and reference lists of recent reviews and meta-analyses were investigated manually. Congress abstracts from the American Society of Clinical Oncology, American Society of Hematology (ASH), ESMO, International Conference on Malignant Lymphoma and European Hematology Association meetings were also evaluated. After identifying relevant publications, a further search was conducted on ClinicalTrials.gov registry for open studies (accessed on December 2016). Moreover, a short paragraph at the end of the present manuscript is specifically dedicated to the last breaking news from ASH congress (December 2016).

Brentuximab vedotin

BV is a chimeric anti-CD30 mAb targeting cells expressing CD30, the tumor necrosis factor-receptor family member 8 and Kiel-1 antigen. CD30 is expressed on Reed- Sternberg cells of Hodgkin's disease, in cutaneous anaplastic large cell lymphoma (ALCL), and in type C lymphomatoid papulosis lesions [11]. CD30 is also expressed frequently at various levels on lesions of MF especially during transformation to large cell lymphoma and may be induced by viral infections as an activation marker [12]. Results of one phase II study on the use of BV in CTCL reported that the drug is both active and well tolerated in CTCL and lymphomatoid papulosis, with an overall response rate (ORR) of 73% and complete response (CR) rate of 35%. In particular, fifteen (54%; 95% CI, 31–59%) of 28 patients with MF responded, independently of CD30 expression. In patients with MF/SS, the ORR was 50% (five of 10 patients) in patients with low CD30 expression (<10%), 58% (seven of 12 patients) in patients with medium expression (10–50%), and 50% (three of six patients) in patients with high expression ($\geq$50%). Time to response was 12 weeks (range, 3–39 weeks), and duration of response (DoR) was 32 weeks (range, 3–93 weeks). All patients with lymphomatoid papulosis (n = 9) and primary cutaneous anaplastic T-cell lymphomas (n = 2) responded; time to response was 3 weeks (range, 3–9 weeks), and median DoR was 26 weeks (range, 6–44 weeks) [13]. Another phase II study reported an ORR of 70% in advanced MF/SS with a wide range of CD30 expression levels [14]. Results from the phase III trial of the efficacy and safety of BV vs physician's choice (methotrexate or bexarotene) reported that BV for patients with relapsed and/or refractory CTCL was associated with significantly improved ORR (44%) and CR rate, significantly improved progression free survival (PFS, 13.2 months), decrease in symptom burden, measured by Skindex-29 $\geq$50% reduction by modified severity-weighted assessment tool (mSWAT) in skin disease response was observed in substantially more patients in the BV arm, compared with the physician's choice arm (NCT01578499) [15]. These data provided compelling evidence favoring BV over bexarotene/methotrexate for the treatment of relapsed/refractory CD30-positive CTCL.

Toll-like receptor agonists

Toll-like receptor agonists stimulate the innate immune system to harness an anti-CTCL effect by the production of cytokines such as IFN[alpha] and IL-12.

Case reports of **imiquimod** 5% have shown activity in MF. Early stage MF may have a long course over many years and skin-directed treatments are preferred, but these are limited in number and either maximal doses or loss of response typically occurs forcing the use of systemic therapies. Topical imiquimod 5% is an alternative topical agent for early stage refractory MF and may provide benefit in patients with plaques of MF resistant to other therapies. Similarly to use in basal cell carcinoma and actinic keratosis an inflammatory reaction occurs. However, the high response rate (80%) and possibility of durable CR in refractory disease make it a useful addition to therapeutic options [16].