Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in the western countries. The disease can be quite heterogeneous in terms of clinical behavior with a portion of patients experiencing an indolent disorder with no or late need of therapy, while others more rapidly become symptomatic and require therapy. These patients will eventually relapse and some of them will show no response to the most effective treatments including immunochemotherapeutic combinations. Patients refractory to purine-nucleoside analogue based chemotherapy (“fludarabine refractory CLL”) have a particularly dismal prognosis, with an anticipated survival of 10 months. A number of novel treatments are now becoming available targeting relevant pathogenetic pathways in CLL and showing a promising level of activity in relapsed/refractory patients. Cyclin-dependent kinases (CDKs) act as “master regulators” of the cell cycle and are often overactive in human cancer, including lymphoid malignancies, leading to a loss of checkpoint integrity resulting in uncontrolled proliferation. Selective inhibition of CDKs has become of interest in CLL as it might limit the progression of leukemic cells through the cell cycle and facilitate induction of apoptosis, through a mechanism that is independent of TP53, the major genetic determinant of refractoriness in the disease. A number of inhibitors has been produced and tested in clinical studies showing significant responses in patients with relapsed CLL, including those with bulky lymphadenopathy or high risk genetic features such as TP53 abnormalities (i.e. del (17p)). Characteristic dose limiting toxicity for all compounds tested is hyperacute tumor lysis syndrome (TLS). Though these compounds have probably created less enthusiasm as compared to other novel classes of inhibitors, until CLL remains uncurable, agents with novel mechanisms of action such as CDK inhibitors might well be part of the armamentarium of onco-hematologists when patients undergo multiple relapses. For this reason, while the future of these compounds appeared to be rather uncertain, more recently clinical interest in this class of highly-effective agents has been reinvigorated, with the appearance of novel compounds and the opening of new clinical trials.

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