EXPERT'S COMMENT

Treatment options for peripheral T-cell lymphomas (PTCLs) have increased with the emergence of several new drugs in recent years; however, none have been established as a standard treatment based on randomized clinical trials. In the current case report, re-challenge with pralatrexate (10-propargyl-10-deazaaminopterin; PDX) after forodesine failure induced a response in a patient with relapsed PTCL-not otherwise specified. The mechanism of this phenomenon remains unclear; however, I would like to propose a possible mechanism based on: i) the theoretical principles of cancer growth models, ii) the mechanism of action of each drug and iii) the drug concentration in the blood.

Alternating therapy is a reasonable treatment strategy based on the Goldie–Coldman hypothesis.[1] According to this hypothesis, the probability that cancer contains drug-resistant clones depends on the mutation rate and size of the tumor. Combination chemotherapy is the best strategy to overcome resistance, as it enables the administration of many drugs at an early stage. Although combination drug treatments can be intolerable due to toxicity, alternating therapy enables the administration of multiple non-cross-resistant drugs with tolerable toxicity. In this case, a reduction in the tumor was observed after PDX rechallenge following the failure of forodesine treatment. Forodesine may have some effect on PDX-sensitive clones.

PDX is a novel antifolate that was designed specifically to have a high affinity for the reduced folate carrier, which efficiently internalizes natural folates and antifolates, and has been demonstrated to be highly active in T-cell lymphoma.[2] In contrast, forodesine is a novel purine nucleoside phosphorylase (PNP) inhibitor. Preclinical studies revealed that PNP deficiency increases the dGuo concentrations in plasma and T-cells.[3] An increased concentration of dGuo results in the accumulation of deoxyguanosine triphosphate. This in turn causes an imbalance in the deoxynucleotide pool, which reduces ribonucleotide reductase activity, leading to T-cell apoptosis. This imbalance may increase the anti-tumor activity of PDX.

In the current case, rechallenge with PDX induced both a strong adverse event and an anti-tumor response. This suggests that the blood PDX concentration was high, leading to both desirable and undesirable effects. Although the blood concentration of PTX was not measured, forodesine may have affected its concentration. Dose-adjusted (DA)-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) therapy resulted in relatively higher response and survival rates (response rate, 78%; 2-year progression-free survival rate, 62.5%; and 2-year overall survival rate, 82.4%) in untreated patients with PTCL than a CHOP (cyclophosphamide, prednisone, vincristine and hydroxyl doxorubicin) regimen.[4] DA-EPOCH has been used in dose-adjustment strategies based on the hematopoietic nadir, where pharmacokinetic analyses of etoposide and doxorubicin revealed significant interpatient variation in steady-state plasma concentrations. This strategy is reasonable when there is a sufficient blood concentration.

It will be necessary to develop a regimen with acceptable toxicity based on simultaneous or sequential use of drugs with different non-cross-resistance or different mechanisms of action to achieve stronger antitumor effects. The results of further clinical trials are keenly awaited.

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