COMPARISON OF LYMPHODEPLETING CHEMOTHERAPY REGIMENS AS PRECONDITIONING FOR T-CELL THERAPIES

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Background Lymphodepleting chemotherapy is typically to patients prior to cell infusion to promote expansion, persistence, and function of adoptively transferred engineered T-cells. Various regimens and doses of are used. Lymphodepletion therapy works by multiple mechanisms, including the elimination of sinks for homeostatic cytokines, such as interleukin-7 (IL-7) and interleukin-15 (IL-15), caused by depletion of endogenous lymphocytes. We applied semi-mechanistic mathematical modeling to compare different lymphodepletion regimens by simulating absolute lymphocyte count (ALC) and IL-7 and IL-15 levels in patients at the time of engineered T-cell infusion (table 1).

Methods The developed mathematical model describes pharmacokinetics (PK) of the 2 drugs fludarabine and cyclophosphamide, their effects on lymphocyte (T-cells) depletion, and contribution of T-cells in the degradation of IL-7 and IL-15. PK models and parameters of fludarabine and cyclophosphamide were taken from published models.1 2 These models were used to describe the impact of creatinine clearance (CrCl) on the clearance of both drugs, and were validated against PK data in patients with renal impairment. Fludarabine and cyclophosphamide effects on ALC, IL7 and IL15 were fitted and validated against clinical data reported on monotherapies and their combination.3 4

Results Two regimens similar to regimen 3 but with a reduced dose of fludarabine were tested for patients with mild and moderate renal impairment. The most effective regimen in patients with normal renal function was regimen 1 (fludarabine 30 mg/m²/day for 4 days and cyclophosphamide 1800 mg/m²/day for 2 days) followed by regimen 6 (fludarabine 30 mg/m²/day for 3 days and cyclophosphamide 500 mg/m²/day for 3 days). Regimen 1 resulted in the lowest ALC at the time of T-cell infusion (median = 0.032*10⁹ cell/L). The highest IL-7 level was observed for regimen 1 (median = 28.93 pg/mL), whereas the highest IL-15 level was observed for regimen 6 (median = 19.69 pg/mL). Regimen 2, consisting of two doses of cyclophosphamide, showed substantially higher ALC and lower levels of IL-7 and IL-15. Regimens for patients with renal impairment showed almost the same ALC and cytokine levels as regimen 3.

Conclusions The most effective regimen of lymphodepletion in terms of ALC decrease and cytokines increase was predicted to be fludarabine 30 mg/m²/day for 4 days and cyclophosphamide 1800 mg/m²/day for 2 days. However, there was no substantial difference between tested regimens except regimen 2 showed the lowest efficacy.

REFERENCES

Abstract 338 Table 1 Regimens simulated by the model.

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