Thymidylate-synthase poly-epitope peptide vaccination in pretreated metastatic cancer patients: a multi-arm phase Ib trial


1U.O.C. Oncology and Radiotherapy, Siena
2Medical Oncology Unit Fondazione Tommaso Campanella & Magna Graecia University of Catanzaro, Catanzaro
3U.O.C Microbiologia e Virologia, Azienda Ospedaliera Universitaria Senese, Siena
4Medical Biotecnology Department, Siena
5Farmacia Ospedaliera AOUS, Siena
6Dipartimento di Biotecnologie, chimica e farmacia, Siena
7U.O.C. Radiotherapy, Siena

Thymidylate-synthase (TS) poly-epitope (27-mer) peptide (TSPP) is a vaccine containing the amino-acidic sequences of three CTL epitopes with HLA-A2.1-binding motifs of TS, an enzyme over-expressed in cancer cells, which plays a crucial role for DNA repair and replication and inhibited by 5'-fluorouracil. Preclinical characterization granted the rationale to design a dose-finding multi-arm phase Ib trial (TSPP/VACI) to test in metastatic cancer patients TSPP vaccination alone (arm A) or in combination with the IG1 immunomodulation regimen1 (with GM-CSF scIL2) (arm B) or in combination with the GOLFIG poly-chemoinmunotherapy2 (arm C). This trial was designed to test the safety and immunobiological activity of TSPP vaccination in different therapeutic conditions. Forty-nine pretreated metastatic cancer patients, with a good performance status (ECOG < 2) were enrolled in the study between April 2011 and July 2013 (12 in arm A, 9 in arm B, 29 in arm C). All patients received every 2/3 weeks sc. injections of TSPP/montanide (1:1 emulsion) at escalating dosage [9, 100 µg (DL-1); 9, 200 µg (DL-2) and 31, 300 µg (DL-3)]. Dosage and schedules of IG1 and GOLFIG regimen have been published in previous reports1,2. TSPP resulted safe and its MTD was not achieved. There was no grade 4 toxicity. The most common adverse events were grade 2 dermatological reactions; cough, rhinitis, fever, poly-artralgia, gastro-enteric symptoms and to a lesser extent, moderate hypertension and hypothyroidism. The majority of adverse events recorded in the arm C were related to GOLFIG regimen and consisted G1-2 haematological (16 cases) and gastro-enteric events (12). TSPP vaccination was associated with rise in auto-antibodies and TS-epitope-specific CTL precursors with substantial differences in the expression of regulatory T-cells, CTL subsets, and cytokine functional phenotype among the arms. TSPP vaccination showed evidence of antitumor activity with a disease control rate of 66.7% in arm A, 33.3% in arm B, and 79.3% in arm C with a median PFS of 6.4 (95% CI = 3.66-9.2), 3.69 (95%CI = 1.55-5.82), and 4.93 (95%CI = 3.79-6.065) months respectively, and an OS of 10.98 (95% CI = 7.56-14.4), 5.9 (95% CI = 4.11-7.69), and 11.96 (95% CI = 8.92-14.98) months, respectively. Our findings provide the framework to evaluate TSPP anti-tumor activity in further trials.