Early morning immune checkpoint blockade and overall survival of patients with metastatic cancer: An In-depth chronotherapeutic study

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Résumé

Objectives: Anticancer drug administration timing may greatly affect patient's survival, response and toxicities *(1, 2)*. This time-of-day variability originates from the circadian timing system, that controls most physiological functions of the organism ensuring optimal adaptation to the light/dark cycles on earth. Exploiting this circadian changes, cancer chrono-chemotherapy has been studied for several decades now, addressing treatment optimization by selecting the most beneficial time-of-day for administration. **Recent retrospective studies suggest potential large patient's benefit through proper timing of immune checkpoint blockers (ICB)*(2)*. The association between ICB treatment timing and patient survival, neoplastic response and toxicities was investigated, together with interactions with performance status (PS) and sex. Dedicated mathematical methodologies were developed to study the impact of administration timing on patient outcomes.**
Methods: A cohort of patients with metastatic or locally advanced solid tumors, who received pembrolizumab, nivolumab, atezolizumab, durvalumab, or avelumab, alone or with concomitant chemotherapy, between November 2015 and March 2021, at the Centre Leon Bérard (France), was retrospectively studied. A statistical framework for splitting the patient cohort into either two (i.e., "morning" / "afternoon") or four drug timing groups was developed combining the predictiveness curve method and the restricted mean survival time (RMST) minimization algorithm. For survival analysis, a continuous approach based on a sinusoidal Cox model for the timing variable was further proposed.

Results: 361 patients were investigated (80% non-small cell lung cancer patients, mean (SD) age: 63 (11) years, 39% of women, 83% PS0–1 at first infusion, 19% received concomitant chemotherapy). ICB were administered from 07:25 to 17:21 and optimal morning/afternoon cut-off was estimated to 11:37 by the predictiveness curve method. Such an optimal timing cut-off was then confirmed by the RMST-based algorithm. **Morning infusions were associated with increased OS as compared to afternoon (median 30.3 vs 15.9 months, p = 0.0024; HR 1.56 (1.17-2.1), log-rank p = 0.003). A strong PS-timing interaction was found (PS0-1 patients, HR=1.53 (1.10-2.12), p = 0.011; PS2–3 patients, HR=0.50 (0.25–0.97),**

*Intervenant

p = 0.042). Morning PS0–1 patients displayed increased OS (median 36.7 vs 21.3 months, p = 0.023), partial/complete response rate (58% vs 41%, p = 0.027), and grade1–3 toxicities (49% vs 34%, p = 0.028). Timing differences in toxicities resulted significant only in female patients (women vs men: p < 0.001 vs 0.4).

Next, we challenged the binary definition of morning/afternoon infusion groups in order to account for the continuous and periodic nature of the timing variable. We developed a sinusoidal Cox model to analysis the association between drug timing and patient survival which allowed us to estimate the worst ICB time-of-day infusion **at 13:36 (12:48–14:23). Mortality risk ratio between infusions at worst time-of-day, and at best time within hospital opening hours (i.e. early morning) was equal to 4.8 ((2.3-10.1), p = 0.008). Such periodic model as further validated by comparing its predictions with those obtained when splitting the patient cohort into four timing groups by the RMST** method.

Conclusions: Early morning ICB infusion was associated with increased OS, response, and toxicities in patients with PS0–1 as compared to later infusions within the day. Prospective randomized trials are needed to confirm this retrospective study. Furthermore, we provided new statistical tools for studying the association of drug timing with patient outcomes.

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2. S. Catozzi, S. Assaad, L. Delrieu, B. Favier, E. Dumas, A.-S. Hamy, A. Latouche, H. Crochet, J.-Y. Blay, J. Mullaert, A. Ballesta, P. Heudel, Early morning immune checkpoint blockade and overall survival of patients with metastatic cancer: An In-depth chronotherapeutic study. *European Journal of Cancer* **199**, 113571 (2024).