Isolated limb perfusion for locally advanced melanoma in the era of Targeted Therapies and Immunotherapy

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Background

In transit-metastases (ITM) affect 5-10% of all melanoma patients. The lower limbs are their main site of localization (70%). When lesions are small and few can be treated with surgical excision, when bulky or rapidly recurrent, locoregional and systemic therapies are indicated (Figure 1-3). Before the introduction of systemic therapies, hyperthermic isolated limb perfusion (HILP) was the most effective treatment in case of multiple, bulky, recurrent in transit disease. Several large retrospective studies reported a median overall response rate of 70%-90%, a median complete response of 30%-70% and low/medium local toxicity. This treatment is very effective, can be repeated, and is well tolerated even by elderly patients. In our surgical center for many years, HILP was combined with systemic administration of low-dose interferon alpha 2b (LDI) to prolong the duration of the local progression free survival. Koops et al. demonstrated that HILP is a locoregional treatment that has an excellent local response, but no influence on development of distant metastases. Unpredictably many patients with ITM develop distant disease (5-year overall survival of 30%-40%) and for this reason at present immediately start medical therapy. In fact, immune check point inhibitors (ICI) has demonstrated a significant increase in survival of stage III (unresectable) and IV melanoma patients, even if the main limitation is that we have no data on the subgroup of patients with ITMs. For all these reasons, currently patients with ITM are treated immediately with medical therapy and no longer with HILP, and some of them may also have been treated with systemic therapy and HILP. In fact, we know neither what the efficacy of ICI is on the treatment of in-transit metastases nor the best time to integrate them with locoregional therapies The purpose of this study is to evaluate the interaction, in terms of OS, local DFS and distant DFS, between patients treated only with only HILP and patients treated with HILP and LDI/ICI.

Materials and Methods

This was a retrospective cohort study on 187 patients treated with HILP. All patients who underwent HILP, between June 1989 and September 2021 at University Hospital of Padua (UHP) and Veneto Institute of Oncology of Padua (IOV) for unresectable limb melanoma, were identified from prospectively maintained database. Personal and anamnestic data about the patient, as well as melanoma data were extracted from the electronically available medical records. Patients were divided into two cohorts: patients who underwent HILP alone and patients who underwent HILP associated with immunotherapy (IT). Staging of malignancy has been standardized through the 8th version of the American Joint Committee on Cancer (AJCC). Performance status following the clinical event (development ITM or distant metastasis) was defined according to the Eastern Cooperative Oncology Group (ECOG) system. The local response (CR+PR) was evaluated at 6 weeks post HILP and at 12 weekly intervals, according to RECIST 1.1 criteria. HILP-related local toxicity was assessed by the Wieberdink scale and surgical complications by the Clavien-Dindo classification. All data were extracted from the hospital charts. Data collection included demographics, tumor characteristics, treatment and follow-up information. Follow-up information was extracted from scheduled visits. The duration of the follow-up was calculated from the date of HILP to the date of the last follow-up. Continuous data were summarized as median and interquartile range (IQR). Data were compared between two groups using Mann-Whitney test, Chi Square test and Fisher's test. Overall survival (OS) was calculated from the date of HILP to the date of death or the date of the last visit. Disease specific survival (DSS) was calculated from the date of HILP to the date of the death due to melanoma.

visit. Local disease-free survival (DFS) was calculated from the date of HILP to the date of ITM/death or the date of the last visit. Distant DFS was calculated from the date of HILP to the date of ITM/death or the date of the last visit. Survival curves were calculated using Kaplan-Meier method and compared by means of log rank test. Multivariable analyses of survival were carried out using Cox regression models including treatment (HILP vs. IT+HILP) and unbalanced characteristics at baseline. Effect sizes were reported as hazard ratio (HR) with 95% confidence interval (CI). All tests were 2-sided and a p-value <0.05 was considered statistically significant. Statistical analysis was carried out using R 4.3

Figure 1-2. In transit metastases
Figure 3. Bulky disease

Results

Overall, 187 patients fulfilled the inclusion criteria (99 treated with ILP and 88 treated with IT+ILP) and were included in the analysis. Immunotherapy included LDI (n=59), ICI (n=12) or both (n=17).

At a median follow-up of 25 months (IQR 9-62) after HILP, 113 patients died (107 from the disease and six due to other causes) and 74 were alive. Overall, 29 patients had ITM, and 96 patients had distant disease during the follow-up.

Overall survival at 3 years after ILP treatment was 43% in ILP group and 61% in IT+ILP group (**p=0.02**). Disease-specific survival at 3 years after ILP treatment was 43% in ILP group and 64% in IT+ILP group (**p=0.02**; Figure 4). Local disease-free survival at 3 years after ILP treatment was 37% in ILP group and 53% in IT+ILP group (**p=0.04**; Figure 5). Distant disease-free survival at 3 years after ILP treatment was 33% in ILP group and 35% in IT+ILP group (p=0.40; Figure 6).

Adjusting for unbalanced characteristics at baseline (age and lymph node involvement), receiving IT+ILP was associated with improved overall survival (HR 0.59, 95% CI 0.30 to 0.89; **p=0.01**) and disease-specific survival (HR 0.56, 95% CI 0.37 to 0.85; p=0.007) compared to ILP alone, while there was no statistically significant difference between the two treatments in terms of local disease-free survival (HR 0.74, 95% CI 0.50 to 1.09; p=0.13) and distant disease-free survival (HR 0.79, 95% CI 0.55 to 1.14; p=0.21).

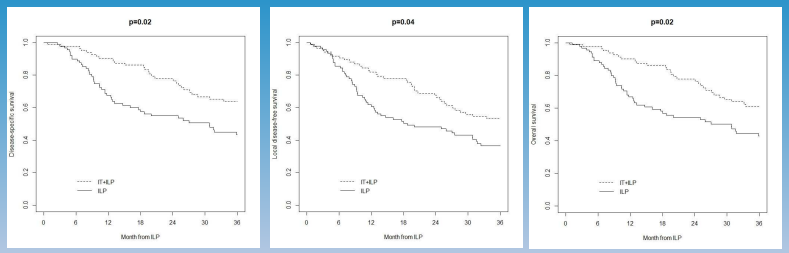

Figure 4. Disease-specific survival in ILP vs. IT+ILP groups.
Figure 5. Local disease-free survival in ILP vs. IT+ILP groups.
Figure 6. Overall survival in ILP vs. IT+ILP groups.

Conclusion

The results suggest a possible synergy between ILP and immunotherapy. In our case series the association between ILP and IT determines a better local response and improved OS than immunotherapy or ILP alone.

ILP remains an effective locoregional treatment option in the era of modern systemic treatments.

Further studies are needed to determine the optimal combination and timing within the association of locoregional treatment with systemic immunotherapy.

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