Clinical Summary Series

HAI Therapy for Unresectable Intrahepatic Cholangiocarcinoma

Long-term outcomes in patients with advanced intrahepatic cholangiocarcinoma treated with hepatic arterial infusion chemotherapy

Cowzer D, Soares K, Walch H, Gönen M, Boucher TM, Do RKG, Harding JJ, Varghese AM, Reidy-Lagunes D, Saltz L, Connell LC, Abou-Alfa GK, Wei AC, Schultz N, Kingham TP, D'Angelica MI, Drebin JA, Balachandran V, Sanchez-Vega F, Kemeny NE, Jarnagin WR, Cercek A.

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"Despite the introduction of immune checkpoint inhibitors and targeted therapies in recent years for select subgroups of patients, the prognosis for many patients [with advanced intrahepatic cholangiocarcinoma] remains grim."

BACKGROUND

Despite the introduction of immune checkpoint inhibitors and targeted therapies for select subgroups of patients, the prognosis for many patients with advanced intrahepatic cholangiocarcinoma (iCCA) remains grim. Standard of care first-line treatment with combined immunotherapy and systemic chemotherapy has improved median overall survival by only 1.3 to 1.8 months. For patients with liver-limited iCCA, hepatic artery infusion (HAI) delivered in conjunction with systemic chemotherapy has been demonstrated to achieve durable long-term disease control and survival.

This report presents long-term follow-up of patients diagnosed with unresectable iCCA who were treated with HAI plus systemic chemotherapy as part of a prospective phase II clinical trial conducted at Memorial Sloan Kettering Cancer Center, along with a retrospective analysis of similarly diagnosed patients who were treated according to routine clinical care outside the trial at the same institution.

Long-term outcomes of prospective phase II study and retrospective analysis of routine clinical care cohort add to accumulating evidence of durable disease control and prolonged survival following hepatic artery infusion (HAI) treatment in patients with unresectable intrahepatic cholangiocarcinoma (iCCA).

TABLE 1

Clinical Characteristics of Patients Treated as Part of Clinical Trial and Routine Care

CHARACTERISTIC	TRIAL COHORT (N = 38)	ROUTINE CARE COHORT (N = 170)
Age at diagnosis, median (range), y	64 (39-81)	63 (30-86)
Sex		
Male	13 (34%)	72 (42%)
Female	25 (66%)	98 (58%)
Eastern Cooperative Oncology Group performance status		
0	18 (47%)	87 (51%)
1	20 (53%)	78 (46%)
2	0	5 (3%)
Prior systemic therapy	3 (8%)	61 (36%)
Histologic grade		
Well	3 (8%)	3 (2%)
Moderate	19 (50%)	87 (51%)
Poor	14 (37%)	61 (36%)
Unknown	2 (5%)	19 (11%)
Dominant tumor size prior to treatment, median (range), cm	8.3 (1.7-24.8)	8.4 (1.0-19.5)
Regional lymph node involved	18 (47%)	86 (51%)

METHODS

A single-arm phase II study of HAI-floxuridine plus systemic gemcitabine and oxaliplatin was conducted in patients with unresectable iCCA between May 20, 2013 and June 27, 2019. Detailed eligibility criteria, protocol and treatment procedures, and landmark analyses at a median follow-up of roughly two and a half years were reported in 2020.[1] This report presents outcomes at a median follow-up of almost six and a half years.

The accompanying retrospective analysis assessed outcomes of patients with biopsy-proven locally advanced unresectable iCCA treated with HAI-floxuridine (with or without systemic chemotherapy) as part of routine care outside the clinical trial from 2000 to 2020.

The primary outcome measure was 6-month progression-free survival (PFS). Overall survival (OS) from the time of pump placement was a secondary measure. Tissue-based genomic sequencing was performed in a subset of patients with the intent of correlating molecular alterations with PFS.

RESULTS

A total of 38 patients were included in the clinical trial cohort; 170 patients were included in the routine care cohort. Clinical characteristics of the cohorts are summarized in Table 1.

PROSPECTIVE CLINICAL TRIAL UPDATE

All patients in the phase II trial received HAI-floxuridine in conjunction with systemic gemcitabine and oxaliplatin.

At a median follow-up of 76.9 months, 6-month disease-control rate was 90% with 12-, 18-, and 24-month disease-control rates of 42%, 24%, and 13%, respectively. Median PFS was 11.8 months, and median liver-specific PFS was 11.9 months. Median OS for patients treated on-trial was 26.8 months, and 1-, 2-, and 5-year OS rates were 89.5%, 55%, and 21%, respectively (Figure 1).

Following progression on HAI plus gemcitabine-oxaliplatin, 29 patients (81%) received at least one line of post-protocol therapy, and 12 continued HAI alone or in combination with an alternative systemic therapy. Five patients were treated with IDH1 inhibitors.

[1] Cercek A, Boerner T, Tan BR, et al. Assessment of hepatic arterial infusion of floxuridine in combination with systemic gemcitabine and oxaliplatin in patients with unresectable intrahepatic cholangiocarcinoma: a phase 2 clinical trial. *JAMA Oncol*. 2020;6(1):60-67.

ROUTINE CLINICAL CARE COHORT RESULTS

Among the routine care cohort, 35% of patients were treated with HAI monotherapy; 65% were treated with HAI with concomitant systemic therapy. The median number of HAI cycles received was 8 (range 1-58).

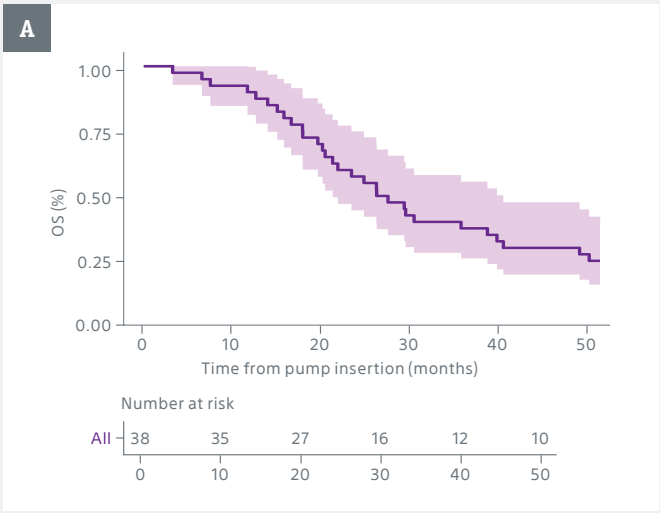
Median PFS for routine care patients who received at least 1 cycle of HAI was 7.93 months. Median PFS did not differ between patients who received HAI monotherapy vs. HAI plus systemic therapy.

Absence of lymph node involvement did not significantly impact PFS (11.1 months vs 7.3 months, p = 0.07). In patients with lymph node involvement, PFS did not differ between those treated with HAI plus concurrent systemic therapy and those treated with HAI alone (7.7 months vs 6.7 months, p = 0.26).

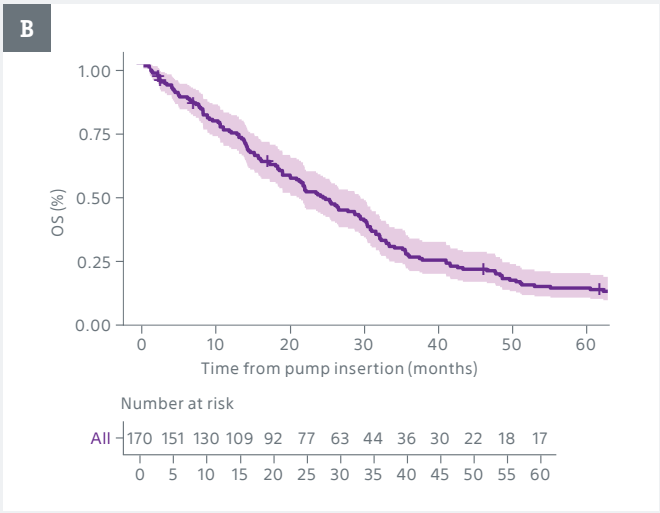
Median OS for patients who received at least 1 cycle of HAI was 22.5 months from the time of HAI pump implantation with no difference in survival between those who were treated with HAI alone vs. HAI in combination with other agents (22.4 months vs 24.0 months; p = 0.60) or between those treated with systemic therapy prior to HAI pump insertion and treatment compared with those not (19.5 months vs 24.9 months, p = 0.40). Median OS was significantly improved in patients with lymph node negative disease compared with lymph node positive disease (26.0 months vs 20.5 months; p = 0.03). Among patients with lymph node positive disease, survival was numerically but not statistically longer in those who received concurrent systemic therapy than those who did not (22.7 months vs 18.9 months, p = 0.32). Estimated 1-, 2-, and 5-year overall survival rates for the routine care cohort were 73.8%, 49%, and 11%, respectively (Figure 1).

FIGURE 1

Overall Survival for (A) Phase II Clinical Trial and (B) Routine Clinical Care Cohorts



A. Phase II clinical trial cohort (N = 38)



B. Routine clinical care cohort (N =170)

	PHASE II CLINICAL TRIAL COHORT (N = 38)	ROUTINE CARE COHORT (N = 170)
mOS	26.8 months	22.5 months
1-Year OS	89.5%	73.8%
2-Year OS	55%	49%
5-Year OS	21%	11%

OS = overall survival

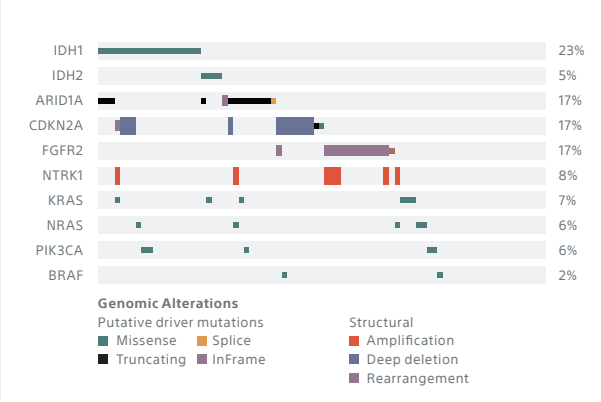
IMPACT OF GENOMICS ON CLINICAL OUTCOMES

A total of 83 patients (35 clinical trial, 48 routine care) underwent genomic sequencing of at least one tissue sample. Median tumor mutational burden was 2.6 muts/Mb. No patient had microsatellite instability. The most common mutations detected are presented in Figure 2.

Median PFS did not differ between patients with IDH1 and 2 mutations vs wild-type (11.9 months vs. 10.2 months, p = 0.92) or FGFR2 fusions vs no structural variant in FGFR2 (14.3 months vs 11.0 months, p = 0.23). Mutations in *KRAS* (6.92 months vs 11.67 months) and TP53 (7.6 months vs 11.7 months) had a numerically worse PFS than those with wild-type disease, although not statistically significant. Alterations in the TP53 (8.13 months vs 11.9 months, p = 0.39) and cell-cycle (7.62 months vs 11.9 months, p = 0.038) pathways were associated with worse median PFS, whereas RAS-RTK and PIK3CA pathway alterations were not.

FIGURE 2

Oncoprint of most commonly detected genetic alterations



LIMITATIONS

Study limitations of the phase II clinical trial include a small sample size and lack of a control group. The routine care cohort analysis is limited by its retrospective nature. It is also important to note that the routine clinical care cohort had a higher proportion of pre-treated patients than the clinical trial cohort (36% vs 8%). Finally, molecular analysis was limited by the small size of the genomic subset.

CONCLUSION

Taken together, results of the prospective phase II study and retrospective analysis of routine clinical care underscore the ability of HAI to achieve durable long-term disease control and prolonged survival in patients with advanced, unresectable iCCA. These results are consistent with prior reports and further substantiate the clinical benefit of HAI in the treatment of unresectable iCCA.

"In conclusion, our study provides valuable evidence of the clinical benefit of hepatic artery infusion with floxuridine in combination with systemic gemcitabine and oxaliplatin for unresectable intrahepatic cholangiocarcinoma."

TAKEAWAYS

- This update to the phase II trial results initially published in 2020 is the longest available follow-up of patients with unresectable iCCA treated with HAI plus systemic chemotherapy.
- At a median follow-up greater than 6 years, HAI combined with systemic chemotherapy achieved durable disease control (PFS of 11.8 months), with median survival of 26.8 months and 1-, 2-, and 5-year survival rates of 89.5%, 55%, and 21%.
- Retrospective analysis of patients treated outside of the trial setting according to routine clinical care reinforced promising PFS and OS following HAI treatment in a sample of unselected patients with advanced, unresectable iCCA.

"…a 5-year overall survival rate of 21% [underscores] the potential for long-term durable disease control with hepatic artery infusion plus systemic chemotherapy…"