Targeted Therapy for Resistant Cholangiocarcinoma with Bevacizumab or Cetuximab Added to Failed Cytotoxic Drug Cores

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Abstract. *Background: Addition of bevacizumab/targeted therapy to cores consisting of four to five previously failed cytotoxic drugs employed at low/moderate dosages has produced third- and fourth-line regression of refractory gastric and ovarian cancer. Targeted therapy added to cores of previously failed drugs has similarly produced responses of refractory pancreatic cancer. Patients and Methods: The aim of the present study was to evaluate the addition of targeted therapy to failed cores for patients with end-stage disease. Patients all had end-stage measurable cholangiocarcinoma and active progression during treatment with cores. Targeted therapy, bevacizumab or cetuximab, at standard dosages and schedule was added to the failed cores, which consisted of: gemcitabine, fluorouracil, leucovorin and irinotecan on day 1, and a platin with/without docetaxel on day 2, each at its prior dose and schedule. Electronic medical records facilitated identification of patients for intent-to-treat analysis. Results: All 13 patients had measurable disease; all standard cytotoxins had been used and failed before the start of treatment with targeted therapy added to the cores. The response rates according to the Response Evaluation Criteria in Solid Tumors and response duration range were: bevacizumab cores: 3/6, 6 to 19 months, and cetuximab cores: 5/7, 10 to 28 months. Responses produced clinical benefit and one late neoadjuvant R0 resection. There were no limiting hematological adverse events due to the cores. Limiting adverse events were hypertension in two patients and an easily controlled duodenal ulcer in one. Conclusion: Bevacizumab cores and cetuximab cores both produced response rates which satisfy phase II criteria for further investigation. As cores, failed cytotoxic drugs, many at one-quarter to half of their standard doses have been found to produce synergistic benefit in combination with targeted therapy for end-stage patients in four diseases. Co-treatment with no longer active cytotoxic core drugs can demonstrate efficacy attributable to the targeted therapy. This approach is a worthy, cost-effective fast-track registration strategy and distinctly different from trials testing primary treatment.*

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Drug 'cores' consist of four to five cytotoxic drugs at low/moderate dose each of which can be synergistic with each of the other drugs in the core and also with selected drugs added to the core. Drugs for such cores were selected for empirical use based on disease-specific prior laboratory *in vitro* screening of a panel of viable human tumors taken directly from patients and translational clinical experience. When used in cores, there was neither need for the drugs to be individually active nor need to be used at conventional high dosages. As designed, the core provides each member drug with three or four synergistic partners, and the opportunity to reverse resistance to each drug (1).

When targeted therapy (TT) is added to the core, one or more, of each of the cytotoxins, gemcitabine (G), fluorouracil (F), irinotecan (I), oxaliplatin (O) and docetaxel (D) can improve its efficacy (2, 3).

Core therapies have increased the disease-specific activity of moderate doses of irinotecan, docetaxel and possibly mitomycin-C (MMC), each of which had failed as high-dose single agents in prior disease-specific phase II trials (1, 4-8). Herein, we describe the use of TT–cores as a last resort treatment for patients with cholangiocarcinoma (CCA). In experience with end-stage gastric, ovarian, and pancreatic cancer, TT–cores increased the survival of many patients due to the length of high quality responses (2, 3, 7, 9).

Patients and Methods

Patients had prior treatment in sequence with standard doses of GO or GX (capecitabine) then GFLP or GFLO then GFLIO then GFLIO plus D with/without MMC. The TT, either bevacizumab or cetuximab standard dose and schedule (Table I) was added to the core as a last resort therapy, based on urgent need for response, after measurable serial failure of the cores. Bevacizumab or cetuximab was selected based on off-label availability of the TT, insurance approval, (perceived) relative safety of one TT *vs*. the other (for the individual patient) and absence of Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation in the case of cetuximab.

Eligibility satisfied standard Institutional Review Board and cooperative group criteria: reasonable expectation of safety, National Cancer Institution Toxicity criteria of grade 0-2 organ function and consent. Patients all had a poor prognosis (measurable, resistant, progressive, high-grade, non-papillary, high-volume CCA). Patients were ineligible if they had contraindications to a drug, required recent (within two weeks) hospital care or intravenous support, or had complications of disease which were not likely to be reversible with reduction in the size of their tumors.

Electronic records (EMRs) included entries for disease and drug for every patient in the practice presenting for an initial visit, each visit and each use of any chemotherapy or any TT. The EMRs included RECIST response findings, radiologist-reviewed computed tomographic images, serial tumor markers (cancer antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) q3-4w) and objective adverse events (AEs); these findings were entered in real time. Monitoring included baseline tests weekly complete blood count q2w metabolic profile and serial, initial, q6w ×2, and then q12w computed tomography or magnetic resonance imaging.

Special preventative efforts for safety and quality of life included mouth care, gastrointestinal care and low roughage diets. Stop-go use of TT was used as needed with low thresholds for brief stops to allow recovery from gastrointestinal AEs due to any reason, disease, chemotherapy or TT.

Treatment is shown in Table I and includes dose adjustment described elsewhere (7, 10).

This was an intent to treat analysis. There were no exclusions of patients given TT for CCA.

Results

There were no perforations or cytopenia with infections. Nadirs were uncomplicated. Limiting AEs, complications, included hypertension twice (both recurrent on re-challenge) but again reversible with discontinuation of bevacizumab. One patient had an ulcer of the duodenum; bleeding was brief and endoscopically controlled; predisposing factors included liver transplant and portal hypertension. Cetuximab produced 3+ facial edema; a Korean male, required cetuximab dose reduction three times and intermittent breaks, stop-go, in TT.

Both bevacizumab and cetuximab produced responses when added to cores. RECIST response rates and duration (range) for bevacizumab cores produced responses for three out of six patients, of 6 to 19 months' duration, and 24+ months' stable disease. Cetuximab cores produced responses for five out of seven patients, of 10 to 28 months' duration (Table I). Responses produced clinical benefit (symptoms, performance status and liver function) and one opportunity to perform a late R0 resection. It was possible to resume stop-go TT, with both bevacizumab and cetuximab (individually) added to ongoing therapy with the core. Anecdotally, resumption of TT sometimes appeared to produce further response and even reverse progression observed during 'stops' of TT.

Discussion

There is promising phase II evidence regarding a role for TT in combination with chemotherapy for CCA (11, 12). Both anti-angiogenic and signal pathway inhibitors can be active *in vitro* and *in vivo* (12-15). These previous trials did not address the feasible number of lines of prior therapy, nor the benefit of low- *vs*. high-dose cytotoxins, nor the benefit of one *vs*. many potentially synergistic cytotoxic partner drugs. Randomized trials of primary TT in combination with standard chemotherapy have to date failed to improve overall survival (16, 17).

The current findings suggest that cores in combination with TT can expand the indications for TT multiline-resistant CCA. This work identified test-worthy cores and test-worthy low doses of cytotoxins. TT cores can sometimes be less costly and safer than TT added to high-dose drug regimens because the choice of drugs and dosage can reduce both the cost of drug and rate of AEs. Moreover, when there are no other less-costly active therapies, the late multidrug-resistant measurable disease setting can be cost-effective because it is ideal for monthly assessment of efficacy as all tumors are measurable. Cores give TTs for CCA second chances, similar to the prior experience with GC and PC, to demonstrate their efficacy against disease which proved difficult (trials failed) when TT was combined with standard regimens (2, 3, 8).

TT–core regimens can be safe. In parallel experience, there were no perforations or other hospitalizations for AEs (3, 7, 8). However TT–cores were used with expanded precautions, which may have contributed to their safety; measures included tight dosage titration of the individual cytotoxins and early preventative intervention such as, brief stops, for mild and moderate gastrointestinal AEs. Asymptomatic radiological evidence of enteritis or colitis also prompted stops. Stops were reversible. The ability to safely stop and resume TT with further benefit identifies the stop-go approach as test-worthy with both therapeutic and cost–benefit research objectives.

For 70 patients, in a series comprised entirely of patients with high-risk pathology and advanced active CCA, cores produced a median survival of over 3 years (20). The TT was not responsible for the overall survival (given its infrequent use due to limited coverage of cost by third parties), nor was

Table I. *Targeted therapy for end-stage cholangiocarcinoma.*

Day	Drug *q2w*	mg/m^2	mg/m^2	mg/m^2	AE	Dose Modification %
1	Bevacizumab	Std	Std	-	GI, oral, renal, HTN	50
1	Cetuximab	-	-	Std	GI, skin	20
1	Gemcitabine	500	400	400	Plts, WBC, GI, skin, renal*, hepatic*, pulmonary*	20 *50
1	Leucovorin	300		300	-	
1	Fluourouracil/24 h	1,200	1,000	1,000	GI, oral, skin	20
1	Irinotecan	80	60	60	GI	25
2	Leucovorin	250	250	250	-	
2	Docetaxel	-	25	25	See gemcitabine	20
2	Oxaliplatin	40	30	30		
2	Mitomycin-C	-	6	+/– 6	Pulmonary, renal, hepatic	50%

Bevacizumab was given at a standard (std) dosage of 10 mg/kg q2w as was cetuximab, 400 mg/m^2, loading, and 250 mg/m^2 qw. When docetaxel was added, other drugs were reduced by 20% of their current dosages. Initial dosage of docetaxel was 25 mg/m^2; with history of prior limiting thrombocytopenia, 15 mg/m^2; with cetuximab, 20 mg/m^2. Initial dosage of mitomycin-c was 6 mg/m^2, 10 mg maximum total; with history of limiting thrombocytopenia, 3 mg/m^2 with cetuximab 4.5 mg/m. . Fluorouracil given as a 24 hour continuous infusion, was increased in 200 mg/m^2 steps, to a maximum of 1,600 mg/m^2. See text for dose modification to avoid grade 2 gastrointestinal and skin adverse events and achieve absolute neutrophil count 1,500-1,000 mm^3, or platelets 125-75/μl. See text for details of dose escalation. For each drug re-escalation was allowed in half steps every forth week but not to exceed the initial maximum shown in Table I. *Dose escalations were not allowed after renal or hepatic AEs.

Table II. *Refractory cholangiocarcinoma treated sequentially with gemcitabine (G), fluorouracil (F), irinotecan (I), oxaliplatin (O) and docetaxel (D) and targeted drugs.*

Patient	Gender	Age, years	Agent	Response	Adverse event	Started chemotherapy	Started agent	Date stopped	PFS (months)
1C	M	54	Cetuximab	Yes	Moderate rash	10/2007	10/2009	3/2012	17
2C	M	62	Cetuximab	yes	ns	10/2007	10/2009	2/2012	28
3C	M		Cetuximab	Yes	ns	03/2008	11/2009	8/2010	10
4C	M		Cetuximab	Mixed	ns	11/2009	11/2010	3/2011	4
5C	F	59	Cetuximab	Yes	ns	12/2008	12/2011	11/2012	12
6C	F	39	Cetuximab	Mixed	Severe HTN	02/2011	07/2011	11/2011	4
7C	M	59	Cetuximab	Yes	Severe rash	01/2012	05/2013	04/2014	10
1B	F	54	Bevacizumab	Stable	ns	08/2009	12/2009	12/2013	48
2B	F	60	Bevacizumab	Yes	ns	03/2010	11/2011	6/2013	19
3B	F	53	Bevacizumab	Yes	GI bleed	12/2011	11/2012	10/2013	11
4B	F	51	Bevacizumab	UE	Severe HTN	09/2011	12/2012	1/2013	0
5B	F	46	Bevacizumab	UE	Severe headache	11/2010	11/2013	11/2013	0
6B	F	67	Bevacizumab	Yes	ns	3/2010	1/2014	07/2014	6

M: Male; F: female; PFS: progression-free survival; ns: not clinically significant, Mixed: response clinically unsatisfactory, UE: unable to be evaluated.

it due to slow-growing tumors. In the overall series, under similar circumstances progression was rapidly fatal; subsequent median overall survival was 2-3 months.

The mechanisms of core and TT–core synergistic interactions remain unknown, many may contribute simultaneously: bioavailability, biochemical modulation and possibly metronomic and collateral sensitization. The high rate of stable disease in the gemcitabine plus cetuximab experience suggests that when a cytotoxin is combined with TT, one can produce a high rate of biochemical modulation (21).

This hypothesis-generating analysis sought to identify test-worthy TT drug development strategies. A test-worthy late option does not replace testing of either early TT or TT in combination with standard dosages of chemotherapy. TT–cores are additional (new) options for development of both TT and otherwise ineffective (or no longer effective) or unsafe (at high dose) drugs. They are additional and new options as both last resort therapies and for management of crises.

Late use appears to be an attractive strategy for a fast track overall survival test. The patients had life-threatening CCA

with no further established treatment. Each month of use of the TT–cores, with continued response, probably improved overall survival and quality of life for more than half of the patients. Expected median survival for similar untreated patients is 3-4 months and the range is less than 6 months. High response rates, which very probably improved overall survival, were also observed in parallel trials of end-stage gastric and ovarian cancer (3, 7).

Controlled trials of TT–cores are needed to fully address response rates and overall survival. Both phase II and III trials deserve high priority because there are few promising therapy options for patients with end-stage CCA.

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