CONSENSUS TREATMENT GUIDELINES FOR URGENT SYMPTOMS IN CHOLANGIOCARCINOMA (CC) PATIENTS (PTS) WITH BILIARY STENTS OR CATHETERS USING THE MODIFIED RAND/UCLA DELPHI PROCESS

452

Iyer R,[1] Acquisto S,[2] Bridgewater J,[3] Choti M,[4] Hong T,[5] Kis B,[6] Mead P,[7] Parikh N,[8] Roberts L,[9] Roberts R,[10] Sicklick J,[11] Siegel R,[12] Whisenant J,[13] Cherepanov D,[14] Broder MS,[14] Valle JW[15]

[1] Roswell Park Cancer Institute, [2]The Bili project Foundation, [3] UCL Cancer Institute, [4]UT Southwestern, Dallas, [5]Dana Farber/Harvard University, [6]H. Lee Moffitt Cancer Center and Research Institute, [7]Memorial Sloan Kettering Cancer Center, [8] University of Michigan, [9] Mayo Clinic, Rochester, [10]Cook County Health and Hospital System, [11] University of California, San Diego, [12] Advocate Lutheran General Hospital, [13]University of Utah Health Care, [14]Partnership for Health Analytic Research, LLC, [15]University of Manchester

INTRODUCTION

- Cholangiocarcinoma patients with biliary stents or percutaneous biliary drainage catheters often present with fever and or jaundice requiring urgent treatment for which there is no uniform guideline. [1-3]
- Providers who evaluate these patients in an urgent setting often find it challenging to determine the cause of acute symptoms. The Cholangiocarcinoma Foundation has provided an emergency biliary card to aid patients and providers to diagnose and treat ascending cholangitis that these patients are at high risk to develop following instrumentation of their biliary tree.[4]
- A systematic methodology for group decision-making, such as the RAND/UCLA modified Delphi process [5] has previously been used to develop medical management recommendations.

OBJECTIVE

To develop a consensus on medical treatment of urgent symptoms in cholangiocarcinoma patients with biliary stents or catheters using the RAND/UCLA modified Delphi panel process

METHODS

The modified RAND/UCLA Delphi process involved recruitment of physician experts, development of patient scenarios, collection of ratings, statistical summary of panel agreement, and development of consensus statements.[3]

Physician Experts

- Thirteen physician experts in treatment of NETs, representing various specialties, were appointed to serve on the study steering committee, on the panel, or both; one physician was assigned the moderator role.*

Development of Clinical Patient Scenarios

- Following the experts' review of a summary of published evidence on treatment of biliary emergencies, we collaborated to develop a comprehensive list of key variables used to construct patient scenarios.

* One panelist was able to rate round 1 but not available to participate in round 2 (panelist #14).

Variables Used to Construct Clinical Patient Scenarios

Variable	Range of Values
Bilirubin	Normal or elevated
AST/ALT	Normal or elevated
Temperature	Febrile or Afebrile
White Blood cell count (WBC)	Neutropenia, Normal WBC or Elevated WBC
ECOG performance status	ECOG 0-2 or ECOG 3 (ECOG 4 were felt not to be candidates for aggressive therapy)
Biliary tract imaging findings	New or worsening biliary dilatation or NO new or worsening biliary tract dilatation by imaging
Antibiotic recommendation	Inpatient antibiotics, outpatient antibiotics or no antibiotics recommended
Stent or PTC manipulation	Recommended or not recommended
Therapy	Chemotherapy within last 3 weeks, liver directed therapy or radiation or palliative biliary drainage procedure or chemo > 3 weeks from presentation

Rating of Patient Scenarios

- Experts rated the appropriateness [a] of systematic therapies for each scenario on a scale [b] of 1 to 9.[3]

[a] Appropriate procedure is one in which the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing, without consideration of cost.

[b] A rating of 1 implied that the expected harms greatly outweighed the expected benefits, a rating of 9 indicated that the expected benefits greatly outweighed the expected harms, and a 5 indicated either that the harms and benefits were equal or that the rater was unable to rate the degree of appropriateness for the patient described in scenario.

- Two rounds of ratings were collected: 1st round before and the 2nd round after a face-to-face panel meeting.[c]

[c] At the meeting, panelists discussed 1st round ratings and agreed that recommendations would not differ by whether or not patients were actively treated with chemotherapy. As a result 192 scenarios were not re-rated in the second round.

METHODS

Statistical Summary of Panel Agreement

- For every rated scenario, we calculated two statistics: median of the panelists' ratings and absolute deviation (i.e., distance) from every panelist's rating to the median for the particular scenario.
- Using previously established standards for addressing disagreement,[6] each scenario was scored:
  - *Appropriate*: median rating of 7-9 with no disagreement.
  - *Inappropriate*: median rating of 1-3 with no disagreement.
  - *Uncertain*: median rating of 4-6 with no disagreement.
- Scenarios with >2 ratings from 1-3 and >2 from 7-9 range were considered to have *disagreement* and were not assigned an appropriateness rating.
- All analyses were performed using SAS® version 8.2 (SAS Institute, Cary, NC).

Development of Consensus Statements

- Treatment consensus statements were drafted based on statistical summary of panel agreement in the 2nd round.

RESULTS

Panelist Characteristics

- The 13 panelists were from various geographic regions of the USA (92%) and the UK (8%).
- Specialties of panelists included medical, surgical and radiation oncology, interventional radiology, infectious disease, emergency medicine and gastroenterology.
- Panelists had practiced between 4 and 33 years (median 16.5 years) and self-reported on average that 49.6% of their time was spent seeing patients (range: 20-90%).
- Panelists self-identified themselves as being from a tertiary/academic center (84.6%) or from community centers (15.4%).
- The panelists reported seeing an average of 120 new cholangiocarcinoma patients a year.

Patient Scenarios Scored: 'Inappropriate', 'Uncertain', 'Appropriate', or 'Disagreement'

	Frequency of Agreement			
Agreement	**Freq.**	**Percent**	**Cum. Freq.**	**Cum. Percent**
Inappropriate	87	30.2	87	30.2
Uncertain	73	25.3	160	55.5
Appropriate	98	34.0	258	89.5
Disagreement	30	10.4	288	99.9

- Panelists rated 288 scenarios in the 1st round and rerated them in the 2nd round.
- Panelists also rated 192 scenarios in the 1st round that were not re-rated in the 2nd round as the recommendations would not change if the patients were on chemotherapy or not
- In the 2nd round, 22% (43 scenarios) were rated inappropriate, 7.8% (15) were uncertain, and 29.7% (57) were appropriate. In 40.1% (77 scenarios) there was disagreement.
- Disagreement decreased from 37.5% before the meeting to 10.4% after.

Average Panel Median Rating and Average Absolute Deviation from Median

	1ST Round Results					2ND Round Results				
Variable	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**
Median	480	5.25	2.8	1.0	9.0	288	5.16	2.73	1.0	9.0
Absolute Deviation	480	1.74	0.72	0.0	3.15	288	1.78	0.69	0.15	3.15

- In the 2nd round:
  - average median rating: was 5.16 (range: 1-9), and
  - average distance from median was 1.78 (range: 0.15-3.15).

RESULTS

Example of Rating form for the Appropriateness of Medical Therapies

Table 3. In every cell below, indicate the appropriateness of therapy on a scale 1 to 9

In a patient being actively-treated with chemotherapy (i.e., ≤3 weeks from last chemotherapy) or with liver-directed therapy, internal/external radiation, or endoscopic stent procedure, or who received chemotherapy >3 weeks prior to presentation

Green: Appropriate Blue: Uncertain Pink: Inappropriate Yellow: Disagreement **Value in bold:** Median **(#):** Mean deviation from median

				No new or worsening biliary dilatation by imaging						New or worsening biliary dilatation by imaging					
				ECOG 0-2			ECOG 3			ECOG 0-2			ECOG 3		
Rate the appropriateness of each therapy:				Inpt Abx	Outpt Abx	Stent manipu-lation	Inpt Abx	Outpt Abx	Stent manipu-lation	Inpt Abx	Outpt Abx	Stent manipu-lation	Inpt Abx	Outpt Abx	Stent manipu-lation
Normal bilirubin	Normal ALT/AST	Febrile	Neutropenia	9 (0.3)	5 (1.3)	1 (0.2)	9 (0.0)	4 (1.5)	1 (0.0)	9 (0.1)	2 (0.8)	7 (2.2)	9 (0.2)	2 (1.5)	7 (2.2)
			Normal WBC	5 (1.2)	5 (0.7)	1 (0.2)	7 (1.1)	5 (0.5)	1 (0.0)	7 (1.2)	5 (1.2)	8 (2.1)	8 (1.0)	5 (0.7)	5 (1.5)
			Elevated WBC	8 (1.0)	6 (0.9)	1 (0.5)	8 (0.8)	5 (0.7)	1 (0.0)	9 (0.5)	5 (1.3)	9 (1.8)	9 (0.5)	5 (1.2)	6 (1.9)
		Afebrile	Neutropenia	2 (0.9)	3 (1.7)	1 (0.0)	2 (1.5)	3 (1.5)	1 (0.1)	5 (1.4)	5 (1.7)	5 (2.5)	5 (2.0)	5 (0.9)	3 (2.2)
			Normal WBC	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	5 (2.8)	1 (1.8)	1 (0.8)	3 (2.1)
			Elevated WBC	2 (0.9)	5 (1.2)	1 (0.0)	3 (1.3)	3 (0.7)	1 (0.0)	5 (1.9)	5 (1.5)	5 (2.5)	5 (2.2)	4 (1.3)	5 (2.0)
	Elevated ALT/AST	Febrile	Neutropenia	9 (0.3)	5 (1.9)	1 (0.2)	9 (0.0)	2 (1.5)	1 (0.0)	9 (0.1)	2 (0.7)	8 (1.9)	9 (0.2)	2 (1.7)	7 (1.8)
			Normal WBC	6 (1.5)	5 (0.7)	1 (0.3)	7 (1.2)	5 (0.5)	1 (0.0)	7 (1.1)	5 (1.1)	7 (2.0)	8 (1.0)	5 (0.7)	5 (1.6)
			Elevated WBC	8 (1.2)	6 (1.0)	1 (0.5)	9 (0.8)	5 (1.0)	1 (0.2)	9 (0.5)	9 (0.3)	8 (1.8)	9 (0.5)	5 (1.1)	6 (1.9)
		Afebrile	Neutropenia	2 (2.0)	2 (1.5)	1 (0.0)	3 (2.1)	3 (1.4)	1 (0.1)	5 (2.2)	5 (2.2)	5 (2.8)	7 (2.1)	4 (1.5)	3 (2.2)
			Normal WBC	1 (0.4)	1 (0.3)	1 (0.0)	1 (0.3)	1 (0.0)	1 (0.0)	1 (1.5)	1 (1.2)	5 (2.9)	1 (2.0)	1 (1.0)	3 (2.2)
			Elevated WBC	2 (1.6)	5 (0.8)	1 (0.0)	3 (1.7)	5 (0.5)	1 (0.0)	5 (1.7)	5 (1.2)	5 (2.5)	5 (1.8)	5 (1.2)	5 (2.0)

Definitions:

The term "elevated" in relation to bilirubin, temperature, and ALT/AST means elevated according to the treating physician's institutional, personal, or laboratory standard. For many patients, prior or baseline values should be used to determine whether a laboratory test is abnormal. Similarly, neutropenia implies that, based on the WBC and percentage of neutrophils, the treating physician judges the patient to have an abnormally low neutrophil count.

"New or worsening biliary dilatation" means the treating physician (or a qualified radiologist) is reasonably confident the stent or catheter is obstructed, based on the review of appropriate studies.

Consensus statements that follow apply to patients under the assumption that the patient:

- is out of the immediate post-operative period from any surgical procedures.
- has access to necessary care (e.g., insurance coverage, experienced physicians).
- can be transferred to higher level care if necessary.
- has not signed a do not resuscitate order and is not terminal.
- is not awaiting liver transplantation.
- is given symptomatic treatment (e.g., pain medications, IV fluids), palliative treatment (e.g., palliative surgery), counseling, and emotional support as needed.
- will have his/her disease-directed treatments modified (e.g., from one chemotherapeutic agent to another, from chemotherapy to radiation/liver directed therapy) by an expert oncologist/other specialist after the acute situation is resolved.
- has had all tests necessary to make therapeutic recommendations.
- recommendations for antibiotics do not address peri-procedural use, which is clinician and institution dependent.

The panel recognizes that significant heterogeneity remains within each scenario, and recommends that physicians use clinical judgment when applying any of these consensus statements to patient care.

RESULTS

Consensus recommendations for managing urgent symptoms in cholangiocarcinoma patients

In pts with elevated bilirubin			
	Appropriate	**May be appropriate**	**Inappropriate**
Stent/Tube manipulation	YES		
Inpatient Antibiotics	YES if patient is febrile	If the patient is afebrile but has an elevated WBC or is neutropenic	If the patient is afebrile and has a normal WBC

In pts with normal bilirubin			
	Appropriate	**May be appropriate**	**Inappropriate**
Stent/Tube manipulation	YES if the patient has new or worsening biliary dilatation		
Inpatient Antibiotics	YES if the patient is febrile	If the patient is afebrile but has a new or worsening biliary dilatation and has an elevated WBC or is neutropenic	If the patient is afebrile and has a normal WBC

CONCLUSIONS

- In this study, we show how an expert panel methodology, namely the RAND/UCLA modified Delphi process, enabled participants to systematically quantify the variables that drive decision making and improved overall panel consensus on the appropriateness of management of urgent symptoms in biliary cancer patients not covered in other guidelines.
- The Delphi panel approach resulted in a detailed consensus statement that fills an unmet needed in management of ascending cholangitis in patients with cholangiocarcinoma. Studies of the impact of these guidelines on cost of care and patient outcomes are warranted.

ACKNOWLEDGEMENT

- This work was funded by the Cholangiocarcinoma Foundation.

REFERENCES

1. Eckel F, Brunner T, Jelic S. ESMO Guidelines Working Group. Biliary cancer ESMO Clinical practice Guidelines for diagnosis, treatment and followup. Ann Oncol. 2011 Sep: 22 Suppl 6: vi40-44
2. Catalano O, De Bellis M, Sandomenico F, de Lutio di Castelguidone E, Dlrio P, petrillo A: Complications of biliary and gastrointestinal stents: MDCT of the cancer patient. AJR Am J Roentgenol. 2012 Aug: 199(2):187-96
3. National Comprehensive Cancer network: hepatobiliary Cancers version 1: 2016: 2016
4. www.cholangiocarcinoma.org/biliaryemergencycard
5. Fitch K, Bernstein SJ, Aguilar MS, et al. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica, CA: RAND; 2001:1–123.

Email for questions:
Donna.Mayer@cholangiocarcinoma.org
Renuka.Iyer@roswellpark.org