Interventional Oncology of the Liver

According to Jean-Francois Geschwind, MD, Johns Hopkins University, Baltimore, Maryland, USA, interventional oncology is a hybrid between surgery and radiology, with an emphasis on therapeutic procedures. Precise image guidance is used to access tumors by intraarterial and intratumoral approaches. Drug delivery is improved using techniques, such as drug-eluting microspheres, remote activation, and isolated perfusion.

Most patients with hepatocellular carcinoma (HCC) have intermediate-stage disease at diagnosis. Established therapies for this population are transcatheter arterial chemoembolization (TACE), TACE with drug-eluting beads (DEB-TACE), and radioembolization using yttrium-90 radioactive microspheres. The combination of DEB-TACE plus sorafenib is being evaluated in clinical trials.

TACE significantly improved overall survival (26% to 29%) in studies by Llovet et al. [*Lancet* 2002] (p<0.009) and Lo et al. [*Hepatology* 2002] (p=0.002), with sustained objective response rates (3 to 6 months) of 35% to 39%. These studies led to the adoption of chemoembolization as the treatment of choice for intermediate and advanced HCC. TACE is also established as standard therapy in patients who await liver transplantation.

Improved tumor targeting is achieved with dual-phase CBCT, and response is assessed with 2-dimensional perfusion software. Varela et al. [*J Hepatol* 2007] reported a 75% response rate with DEB-TACE using doxorubicin in 27 patients with Child-Pugh A disease. One- and 2-year survival rates were 92.5% and 88.9%, respectively, at a median follow-up of 28 months. The Prospective Randomized Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by Drug-Eluting Bead Embolization [PRECISIONV; NCT00261378] trial demonstrated significantly lower rates of doxorubicin-related adverse events with DEB-TACE versus conventional TACE (p=0.012) [Lammer J et al. *Cardiovasc Intervent Radiol* 2010]. In a Johns Hopkins Phase 2 study, median survival with DEB-TACE was 26 months in patients with unresectable HCC.

Radioembolization using yttrium-90 microspheres delivers higher-radiation doses to smaller volumes, providing greater tumoricidal effect and minimizing damage to normal tissue. Several studies have demonstrated the utility of radioembolization in patients with a large tumor burden, multifocal disease, or portal vein thrombosis (PVT). A German study on radioembolization reported a median survival of 16.4 and 10.4 months in patients with and without PVT, respectively.

The combination of DEB-TACE plus sorafenib exploits the proangiogenic effects of TACE. The Phase 3 Study of Sorafenib in Patients With Advanced Hepatocellular Carcinoma [SHARP; NCT00105443] demonstrated an overall survival benefit with sorafenib (10.7 months) versus placebo in patients with HCC (7.9 months; HR, 0.69; 95% CI; 0.55 to 0.87; p<0.001) [Llovet JM et al. *N Engl J Med* 2008]. These results led to the Johns Hopkins Phase 2 trial of doxorubicin-eluting LC bead TACE plus sorafenib in patients with unresectable HCC [NCT00844883]. Grade 3/4 toxicity results were not worse with the combination versus sorafenib or DEB-TACE alone. Early results showed a 96% tumor response rate (RECIST) with DEB-TACE plus sorafenib (Table 2). An ongoing ECOG Phase 3 study is recruiting for a randomized, double-blind comparison of TACE with and without sorafenib in patients with unresectable HCC.

Table 2. Tumor Response: Phase 2 Trial of DEB-TACE Plus Sorafenib.

Features	Pre-DEB-TACE	Post-DEB-TACE	Change at 3 weeks (%)	p value
Tumor Size±SD (cm)	7.9±4.3	7.6±4.5	-4	0.79
Tumor Enhancement (%)	85	43.5	-49	<0.01
ADC* (x10^{-3} mm 2/s)	1.2	1.54	25%	0.01
EASL Partial response: 14/26 (54%) Stable disease: 12/26 (46%)		RECIST Stable disease: 25/26 (96%) Progressive disease: 1/26 (4%)		

*ADC measured by functional diffusion weighted MR; Reproduced with permission from JF Geschwind, MD.

TACE is the gold standard. DEB-TACE using doxorubicin has improved efficacy and fewer side effects compared with TACE. DEB-TACE has a growing role, pending outcomes of clinical trials. There is a strong rationale for combining intraarterial therapies with sorafenib, which has demonstrated excellent safety in preliminary results.

Changing Cancer Paradigm After the United Nations Summit

Putting Cancer on the Global Agenda

John Seffrin, PhD, American Cancer Society, Atlanta, Georgia, USA, discussed the historical significance of the United Nations (UN) High-Level Meeting, the outcomes of the May 2013 65th World Health Assembly, the role of nongovernmental organizations (NGOs), and critical objectives to take advantage of the new global cancer paradigm. "We are seeing the beginning of a tsunami of avoidable, often preventable noncommunicable diseases," Dr. Seffrin said. "Cancer could become the number one leading cause of death in the not-too-distant future."

Dr. Seffrin shared that the outcomes document from the UN High-level Meeting essentially says four things: 1) Cancer and

noncommunicable disease will be the health, disease, and disability challenge of 21st century; 2) we have the knowledge and technology to prevent this; 3) economic development and noncommunicable diseases are inextricably linked; and 4) the problem is not one any single sector can solve alone – and the private sector will be particularly crucial. Dr. Seffrin also cited a recent study from the World Economic Forum and the Harvard University School of Public Health that notes the potential for a $47 trillion expected loss in economic output just in the next two decades from noncommunicable disease. The historic UN meeting served as a wake-up call for global leaders, Dr. Seffrin said.

The 65th World Health Assembly recently called for a 25% global reduction in premature deaths from noncommunicable diseases. The UN political declaration stated the World Health Organization (WHO) must develop targets (specific measures that can be used to hold countries accountable), indicators, and goals by the end of 2012. There is strong support for the four main cancer risk factors: tobacco use, alcohol use, unhealthy diet, and physical inactivity.

NGOs are in a position to provide data and evidence that might not be available in governmental and commercial sectors. They can objectively represent and advocate for patients, engage civil society, and take action without restraints from government or commercial entities. The Noncommunicable Disease (NCD) Alliance is the largest health coalition ever formed, with about 2000 participating organizations.

Three objectives for moving forward include a need to leverage the NCD Alliance, inclusion of noncommunicable diseases in the UN millennial goals, and emphasis on the need for action in this arena to ensure world economic stability, prevent suffering, and save lives.

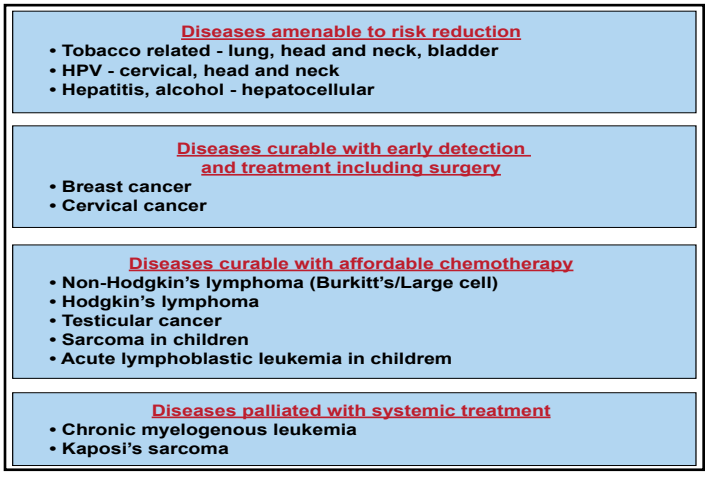
Perspectives in Cancer Care and Future Strategies

Lawrence N. Shulman, MD, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, related his experience in building cancer care infrastructures in low income countries, with a focus on his work in Rwanda. Dr. Shulman emphasized that partnerships among institutions, governments, and industry are keys to success. The cancer care components on which the program focused were education, prevention, screening, early detection, diagnostics, treatment, palliative care, and survivorship.

Dr. Shulman discussed the principles used to guide development of a cancer care program in low-income countries:

1. Develop a cancer care program within the context of the existing healthcare infrastructure.
2. Develop essential services like pathology, surgery, and chemotherapy, to successfully diagnose and treat patients.
3. Develop a supply chain for affordable drugs, vaccines, and other critical services.
4. Develop cancer care services that can be administered by physicians, nurses, and other healthcare workers, with specialist back up via electronic communication.
5. Develop social support, clean water, and adequate nutrition for successful care.
6. Develop a prioritization plan, directing resources to where they are most needed. Cancers where the greatest impact can be made: 1) diseases amenable to risk reduction; 2) diseases curable with early detection and treatment; 3) diseases curable with affordable chemotherapy; and 4) diseases palliated with systemic treatment (Figure 1).
7. Develop specific disease-based protocols to direct interventions and care based on principle #5.
8. Expand partnerships with ministries of health, NGOs, academic cancer programs, private sector entities, foundations, and donors.
9. Develop a research agenda and infrastructure specifically designed to address questions applicable to cancer care in these settings. Prospective studies are needed to understand the effectiveness of interventions.
10. Develop ongoing local training in cancer care.
11. Develop a sustainable program.

Figure 1. Cancers Where An Impact Could Be Made.



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The program's activities in Rwanda have been conducted in close collaboration with the Ministry of Health. National cancer protocols are being developed and approved by the

Ministry. The key to developing a successful program is to integrate prevention, screening, and treatment. Programs need to be developed in parallel with important policy work.

Effects of Prior Bevacizumab Use on Outcomes From the VELOUR Study

Bevacizumab (BEV) is a standard component of frontline therapy and FOLFIRI remains a standard chemotherapy backbone for second-line treatment of metastatic colorectal cancer (mCRC). Aflibercept is a recombinant human fusion protein that acts as a decoy receptor, preventing the interaction of vascular endothelial growth factor (VEGF)-A, VEGF-B, and placental growth factor (PlGF) with their receptors. In the Phase 3 Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Treatment of Patients With Metastatic Colorectal Cancer After Failure of an Oxaliplatin Based Regimen [VELOUR; NCT00561470] trial, aflibercept plus FOLFIRI improved overall survival (OS) compared with FOLFIRI plus placebo in patients with mCRC. This subgroup analysis of the VELOUR trial, presented by Carmen Joseph Allegra, MD, University of Florida, Gainesville, Florida, USA, evaluated the consistency of aflibercept's effect on OS and progression-free survival (PFS) in a prespecified analysis of patients previously treated with BEV.

In the VELOUR study, patients with mCRC were randomly assigned to aflibercept plus FOLFIRI (n=600) or placebo plus FOLFIRI (n=600). The primary endpoint was OS. Patients were allowed only one prior oxaliplatin-containing regimen for metastatic disease. Patients who relapsed within 6 months of completion of oxaliplatin-based adjuvant chemotherapy were eligible. The overall results showed that adding aflibercept to FOLFIRI in mCRC patients previously treated with oxaliplatin-based therapy significantly improved OS and PFS.

For the prespecified subgroup analysis, a p value of <0.1 would indicate a difference in the benefit associated with aflibercept between the prior and no prior BEV groups. Among patients with prior BEV therapy, 186 received aflibercept plus FOLFIRI and 187 received placebo plus FOLFIRI. Among patients with no prior BEV, 426 received aflibercept plus FOLFIRI and 427 received placebo plus FOLFIRI.

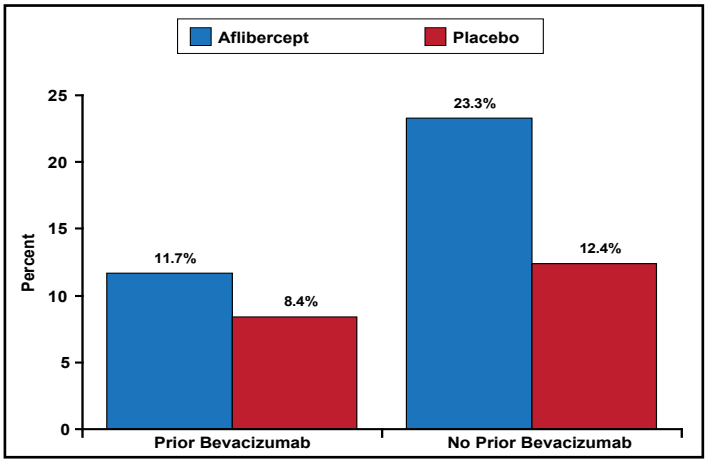
The OS and PFS results were consistent with and without prior bevacizumab. The interaction between the "treatment arm" and "prior bevacizumab" factor was not significant at the two-sided 10% level (p=0.57 for OS; p=0.20 for PFS; Table 1). Among patients with prior bevacizumab, those who received aflibercept had a median OS of 12.5 months versus 11.7 months in patients who received placebo (HR, 0.862; 95.34% CI; 0.673 to 1.104). Among patients with no prior bevacizumab, those treated with aflibercept had a median OS of 13.9 months versus 12.4 months in patients treated with placebo (HR, 0.788; 95.34% CI, 0.699 to 0.927). Response rates in the prior bevacizumab patients were 11.7% in the aflibercept arm versus 8.4% in the placebo arm. Response rates in patients without prior bevacizumab were 23.3% in the aflibercept arm versus 12.4% in the placebo arm (Figure1).

Table 1. Consistency of OS and PFS With and Without Prior BEV.

Prior Bevacizumab			
	Placebo/FOLFIRI (n=187)	**Aflibercept/FOLFIRI (n=186)**	**Δ**
OS (months; 95.34% CI)	11.7 (9.8 - 13.8)	12.5 (10.8 - 15.5)	0.8
PFS (months; 99.99% CI)	3.9 (2.9 - 5.4)	6.7 (4.8 - 8.7)	2.8
No Prior Bevacizumab			
	Placebo/FOLFIRI (n=427)	**Aflibercept/FOLFIRI (n=426)**	**Δ**
OS (months; 95.34% CI)	12.4 (11.2 - 13.5)	13.9 (12.7 - 15.6)	1.5
PFS (months; 99.99% CI)	5.4 (4.2 - 6.7)	6.9 (5.8 - 8.2)	1.5

Interaction between "treatment arm" and "prior bevacizumab" factor was not significant at the two-sided 10% level (p=0.57 for OS; p=0.2 for PFS).

Figure 1. Response Rates.



The safety analysis showed increased anti-VEGF-associated events and general adverse events in the aflibercept arms but no difference between the prior and no prior BEV groups. Rates of adverse events leading to discontinuation were higher in the aflibercept arms, but there was no difference between the prior and no prior BEV groups.

This preplanned subgroup analysis demonstrates consistent trends of increased OS and PFS with aflibercept, regardless of prior treatment with BEV. Prior treatment with BEV does