



## Patients with Hepatocellular Carcinoma Benefit from Changes in Organ Allocation

by Garrett Hisatake, M.D. and Laura Miyashita

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Hepatocellular carcinoma (HCC), or liver cancer, is the most common malignancy arising within the liver and its incidence in the United States has doubled over the last two decades.

Worldwide, it is expected that more than 1,000,000 individuals will develop HCC this year, primarily due to the large population of patients with Hepatitis B and C, although almost any condition that causes chronic liver disease (cirrhosis) increases the risk for liver cancer.

“Because 90% of patients who develop HCC already have underlying chronic liver disease, very few of these patients will have sufficient hepatic reserve to be considered for surgical resection,” says Garrett Hisatake, M.D., a liver surgeon with California Pacific’s Liver Disease Management and Transplant Program. He adds, “For these individuals, liver transplantation remains the only possible chance for cure.”

#### MELD Focuses on Disease Severity

On February 27, 2002, the method of allocating organs to recipients awaiting liver transplantation in the U.S. changed dramatically, as the United Network for Organ Sharing (UNOS) adopted the Model for End-Stage Liver Disease (MELD) to replace the previous allocation policy. The original goal of MELD was to predict one’s chance of mortality from liver disease; the higher the number, the higher one’s three-month mortality. UNOS adopted this allocation policy to ensure that the sickest patients had the highest chance of getting transplanted.

With MELD, additional points are awarded for patients with HCC who meet strict criteria for size

#### MELD Score Provisions for Hepatocellular Carcinoma

Criteria	MELD Score Assigned*
Patients with T1 disease: a single nodule that is $\leq 1.9$ cm.	20
Patients with T2 disease: a single nodule that is 2.0 to 5.0 cm in size, or up to 3 multiple nodules, all $\leq 3.0$ cm.	24

\* Revised in March 2003; assigned score will likely be adjusted again within the next year.



and number of tumors. Specifically, patients with T1 disease (a single nodule that is  $\leq 1.9$  cm) are assigned a MELD score of 20; patients with T2 disease (a single nodule that is 2.0 – 5.0 cm or up to 3 multiple nodules, all  $\leq 3.0$  cm) are assigned a MELD score of 24. For most transplant centers in California, the average MELD score at transplantation is over 30 (the highest score one can get is 40), which is the highest in the nation. That means that patients in California have to be much sicker than in other areas of the country before they will be transplanted, and more of them will die while awaiting transplant. The only other state with similar statistics is New York.

#### More HCC Patients Receiving Transplants

Early results suggest that liver cancer patients have benefited substantially since the inception of MELD, experiencing fewer deaths while awaiting transplantation, a lower dropout rate due to disease progression and a reduction in waiting time after approval for transplantation. The MELD has also affected California Pacific’s Liver Transplant Program. In 2001, prior to MELD’s implementation, 17% of all patients undergoing liver transplantation had liver cancer. Comparatively, in 2003, one year after adopting MELD, this number rose to 46%, nearly tripling the previous year’s total (see graph on p. 3). Physicians expect a similar transplant rate for liver cancer patients in 2004. Currently, HCC patients wait eight months to one year before transplant. In

# Research Underway to Examine Drug Induced Liver Injury (DILI)

Genetic Factors Associated with Drug Metabolism & Liver Injury are Focus of Study

by Maurizio Bonacini, M.D. and Laura Miyashita



**B**ecause relatively little is known on individual risk factors that may lead to liver injury as a result of medication ingestion, California Pacific's Hepatology Research Program has pursued funding to research this topic. This funding, recently made possible through the NIH's National Institute of Diabetes & Digestive & Kidney Disease Branch, is part of a grant distributed to eight medical institutions, including California Pacific Medical Center, University of California San Francisco (UCSF), San Francisco General Hospital and Stanford University. In the Bay Area, the principal investigator is Dr. Tim Davern (UCSF).

"Severe drug-induced liver injury (DILI) is relatively uncommon and often unpredictable," says Maurizio Bonacini, M.D., a hepatologist with California Pacific's

Liver Program who has a special interest in the potential toxicity of drugs and other xenobiotics. He adds, "Our goal is to collect well-established DILI cases and study different genes that might be associated with drug metabolism and liver injury."

The definition of DILI is an elevation of liver tests from normal to greater than 5 times the upper limit of normal, in a temporal relationship with the use of medications. By consensus among the investigators, the cases that this multicenter study will enroll are

associated with any of the following four medications:

- isoniazid (used to treat tuberculosis);
- augmentin (an antibiotic);
- dilantin (an anti-seizure medication); and
- valproic acid (an anti-seizure medication)

In addition, a referring physician's expertise is needed to seek appropriate controls (i.e. patients that took the medications but did not experience liver injury.) The investigators will then ask the patients and controls to give blood for further studies. The plan is to use genetic microarrays to assess whether specific genes are present in patients and absent in controls or vice versa.

During the course of this two-year study, researchers will collect data to prospectively study drug-induced liver toxicity. Another one of the study's goals is the development of a diagnostic scale that could help assess the likelihood that a drug is responsible for liver injury. "Causality assessment—that is, linking a medication to liver toxicity, is often circumstantial," says Bonacini. "Therefore, we hope this research will help us develop a scale to aid practicing physicians in determining the likelihood that a drug is in fact the cause of a liver injury episode," he adds.

*If you have any cases of drug-induced liver injury that may be applicable for this study, kindly contact Maurizio Bonacini, M.D. at (415) 600-1026 or by email at bonacim@sutterhealth.org.*

## Liver Disease Management Services Offered at Outreach Clinics

California and Nevada Clinics Bring Hepatologists to Local Communities

by Laura Miyashita



**A**s part of our ongoing commitment to bring specialized liver disease services closer to patients, California Pacific's Liver Disease Management & Transplant Program offers 17 outreach clinics in California and Nevada. Our hepatologists visit these clinics regularly to evaluate new patients with liver disease and follow those who are awaiting or have undergone liver transplantation.

"We realize that it's much more convenient for patients to see a specialist close to home rather than coming to San Francisco for what can be multiple appointments," says Robert Gish, M.D., medical director of the Liver Disease Management &

Transplant Program. Dr. Gish implemented the Liver Program's outreach efforts more than 10 years ago and since that time, has considerably expanded its reach. Today, patients can see one of California Pacific's hepatologists in the following locations:

- Chico
- East Bay
- Eureka
- Fresno/Clovis
- Las Vegas (2 locations)
- Merced
- Modesto (2 locations)
- Oakland
- Redding
- Reno
- Sacramento
- San Luis Obispo
- Santa Cruz
- Santa Rosa
- Ukiah

For contact information and schedules of these clinics, look online at <http://www.cpmc.org/advanced/liver/physicians/outreach.html>.

# Clinical Trials for Liver Cancer Underway at California Pacific

Therapies Aimed at Blocking Cancer Cell Division and Proliferation

By Robert Gish, M.D. and Ari Baron, M.D.

As the incidence of liver cancer increases in both first world and developing countries, pharmaceutical researchers are looking closely at this disease to develop new systemic therapies. Currently, the only cure for liver cancer is liver transplantation. Therapies such as liver resection and radiofrequency ablation benefit about 20% of patients whose cancer has not reached advanced stages. That leaves 80% of liver cancer patients relying on transplantation, which is limited because of the organ shortage. Of these patients, most currently die within five years due to advanced stage of disease at the time of diagnosis. This population particularly concerns researchers, who are trying to develop new therapies directed at advanced disease.

Among the therapies for liver cancer currently in development include:

Thymosin (also known as thymosin alfa-1, Thymalfasin)

**Developed by SciClone Pharmaceuticals, Redwood City, Calif.**

This injectable medication has a number of specific effects including antiangiogenesis and pleiotropic effects seen in vitro, such as:

- stimulation of immunological functions resulting in increased production of cytokines and receptors;

- increased T-cell proliferation/differentiation; and
- inhibition of viral replication in patients with hepatitis virus infection.

More specifically, increases in NK and CD 4 cells are seen in animals after administration; these cells may also help to combat a variety of cancers. Thymalfasin is currently in a small clinical trial at California Pacific to test safety and hopefully efficacy in patients with hepatocellular carcinoma (HCC) who are not candidates for liver transplantation.

PTK787

**Co-developed by Novartis Pharma AG and Schering AG**

This new agent for HCC is in a Phase I/II clinical trial at California Pacific Medical Center, the only site in the nation for the study. PTK787 is an oral medication taken once a day to inhibit the intracellular tyrosine kinase of the VEGF pathway. The molecule's effect is to block angiogenesis and thereby decrease blood supply to the tumor. It has activity in a broad range of malignancies and California Pacific is examining its use for both HCC and colon cancer.

Nolatrexed (Thymitaq®)

**Developed by EXIMIAS Pharmaceutical Company, Berwyn, Pa.**

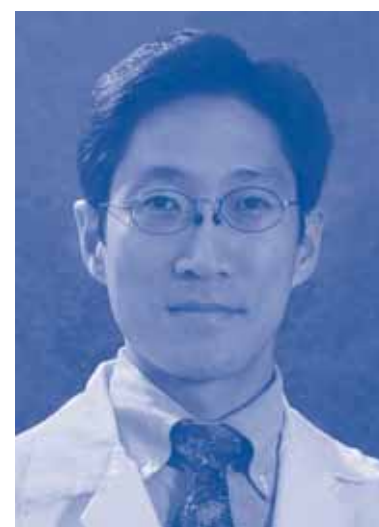
California Pacific is involved in a full Phase III trial of this new medication, which is the largest randomized controlled study of HCC ever performed. Thymitaq blocks the key enzyme of cancer cell division—thymidylate synthetase—thus blocking cell division. This is an advanced compound that is not polyglutamated and, therefore, easily transported into cancer cells. The compound showed survival superiority to adriamycin (doxorubicin) in three Phase II trials. The safety data to date also looks encouraging and the current international trial is more than 75% enrolled.

California Pacific's Hepatology & Gastroenterology Research Program works in conjunction with Pacific Hematology Oncology Associates to pursue clinical trials that may benefit HCC patients. For details on our clinical research studies, contact Pacific Hematology Oncology Associates at (415) 923-3012 or our Hepatology & Gastroenterology Research Program at (415) 600-1100.

## New Surgeon Joins Liver Disease & Transplant Team

Dr. Garrett Hisatake, M.D. recently joined California Pacific's Liver Disease Management & Transplant Program from UCLA Medical Center. He is performing liver and kidney transplants and hepatobiliary surgery. Dr. Hisatake has special interests in living donor liver transplantation, transplantation for malignant diseases and minimally invasive surgery. Prior to this position, Dr. Hisatake served as Clinical Instructor of Surgery and Transplantation at UCLA Medical Center. He received his medical training at the University of Utah and the University of Rochester/Strong Memorial Hospital.

To contact Dr. Hisatake or our surgical team, please call (415) 600-1010.



Surgeon Garrett Hisatake, M.D.

MELD, continued from page 1

comparison, patients with cirrhosis but no HCC typically wait two years.

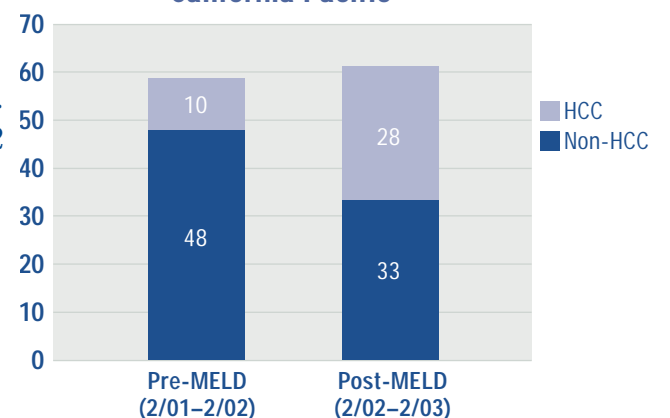
"The MELD has clearly benefited patients with hepatocellular carcinoma," says Dr. Hisatake. "It has dramatically improved organ allocation to patients who previously had few or no options for treatment," he explains.

According to Hisatake, "By selecting those patients whose tumors fall within the size limits, we can continue to offer this life-saving

therapy to those patients who will have the greatest chance for long-term success."

Even with transplantation, however, recurrence of HCC is a real problem, says Hisatake. He explains that patients with small tumors (2 cm) will have rare HCC recurrences (<10%) while patients with large tumors (>5 cm) or multiple tumors have >50% recurrence. Because of these figures, the size criteria are particularly strict in the MELD score calculation, and the scores associated with T1 and T2 disease are under ongoing review by UNOS.

Liver Transplant Cases at California Pacific



# Web Site Offers Clinical Pathways and Patient Information

The Liver Disease Management & Transplant Program Web site (<http://www.cpmc.org/liver>) is a valuable source of information for both physicians and patients. Among the information you can find on this site includes:

**For physicians (<http://www.cpmc.org/advanced/liver/physicians/default.html>)**

- Hepatitis C Clinical Pathway
- Liver Cancer Clinical Pathway
- Liver Biopsy Management Guideline Protocol

**For patients (<http://www.cpmc.org/advanced/liver/patients/default.html>)**

- Liver Cancer Diagnosis and Treatment Overview
- Hepatitis C Questions and Answers
- Liver Biopsy, ERCP and TIPS Shunt Overviews
- Drugs and Herbal Medications that Can Cause Liver Disease
- Living with Your New Liver (transplant manual)

Additionally, our *Liver & GI Review* newsletters are online, as well as contact information and schedules for our outreach sites, clinical trial information and more. As new pathways and patient education materials become available, they are added to this site, so continue visiting for the latest information!



## Liver Disease Management and Transplant Program

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