There is ongoing progress in the understanding of the molecular basis and subgroups of pancreatic cancer, but therapeutic target alterations are rare and treatment options are still mainly based on classic cytotoxic drugs. In *The Lancet Gastroenterology & Hepatology*, Jean-Bapiste Bachet and colleagues[8] report the findings from their non-comparative, randomised first-line phase 2 trial in 114 previously untreated patients with metastatic pancreatic cancer, assigned (2:1) to either the experimental combination of simplified leucovorin and infusional fluorouracil plus nab-paclitaxel or to gemcitabine plus nab-paclitaxel. The primary endpoint of more than 50% of participants in the leucovorin and fluorouracil group being alive and progression free at 4 months was reached (at 4 months, 40 [56%, 90% CI 45–66] of 72 patients in the leucovorin and fluorouracil group were alive and free from disease progression; 21 [54%, 40–68] of 39 patients in the gemcitabine group were also alive and progression-free at 4 months). Both regimens were tolerable, although their toxicity profiles differed markedly: more hepatic and haematological toxicities occurred in the gemcitabine group and more febrile neutropenia, mucositis, paresthesia, alopecia, and hand–foot syndrome occurred in the leucovorin and fluorouracil group. Overall, the study results warrant further study of the simplified leucovorin and infusional fluorouracil plus nab-paclitaxel combination.

For patients with pancreatic cancer who are intolerant or have disease progression while on adjuvant or palliative gemcitabine, simplified leucovorin and infusional fluorouracil plus nab-paclitaxel could be considered an additional treatment option beyond the combinations of infusional fluorouracil–folinic acid with oxaliplatin[9] or nanoliposomal irinotecan.[10] Evidence from clinical trials suggests that gemcitabine is equally as efficacious as infusional fluorouracil–folinic acid; because of the different toxicity profiles of leucovorin and fluorouracil plus nab-paclitaxel and gemcitabine plus nab-paclitaxel regimens, each with a low risk of grade 4 adverse effects, both might provide the backbone for experimental multiple-drug combinations in advanced pancreatic cancer.

Hanno Riess
Department of Hematology and Oncology, University Hospital Charité, Berlin, D-10117, Germany
hanno.riess@charite.de

I have received fees for advice and talks from Celgene and Shire.

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; **66:** 7–30.
2 Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine *vs* observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007; **297:** 267–77.
3 Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013; **310:** 1473–81.
4 Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017; published online Jan 24. DOI:10.1016/S0140-6736(16)32409-6.
5 Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreatic cancer: a randomized trial. *J Clin Oncol* 1997; **15:** 2403–13.
6 Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364:** 1817–25.
7 Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369:** 1691–703.
8 Bachet J-B, Hammel P, Desramé J, et al. Nab-paclitaxel plus either gemcitabine or simplified leucovorin and fluorouracil as first-line therapy for metastatic pancreatic adenocarcinoma (AFUGEM GERCOR): a non-comparative, multicentre, open-label, randomised phase 2 trial. *Lancet Gastroenterol Hepatol* 2017; published online Feb 27. http://dx.doi.org/10.1016/S2468-1253(17)30046-8.
9 Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol* 2014; **32:** 2423–29.
10 Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 2016; **387:** 547–57.

Direct-acting antivirals for acute HCV: how short can we go?

Published Online
February 27, 2017
http://dx.doi.org/10.1016/S2468-1253(17)30043-2
See Articles page 347

Treatment for individuals with hepatitis C virus (HCV) infection has evolved rapidly, with combinations of two or more different classes of direct-acting antivirals for 8–12 weeks achieving sustained virological response (SVR) in more than 95% of treatment-naive, non-cirrhotic individuals with chronic HCV infection.[1–3]

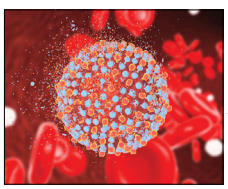
In this context, the optimal management of acute HCV infection is uncertain. With little data available, recent international guidelines support a fairly conservative approach, with the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD–IDSA) guidelines advocating the same regimens for acute HCV as recommended for chronic HCV, while the European Association for the Study of the Liver (EASL) guidelines suggest sofosbuvir plus an NS5A inhibitor for 8 weeks, with a longer duration of

12 weeks for those with HIV or baseline HCV RNA higher than 1 000 000 IU/mL.

Trials are underway to fill this evidence gap, assessing short duration direct-acting antiviral regimens in acute (<6 months) and recent (<12 months) HCV infection.[4-6] Preliminary results following 4 weeks and 6 weeks of sofosbuvir–ledipasvir in acute genotype 1 HCV monoinfection have been encouraging.[4,6]

In *The Lancet Gastroenterology & Hepatology*, Jürgen Rockstroh and colleagues[7] have further advanced the field by examining the efficacy and safety of 6 weeks of sofosbuvir–ledipasvir for acute HCV infection in HIV coinfection.[7] All 26 participants were men who have sex with men with well-controlled HIV and HCV genotypes 1a or 4. Most were asymptomatic, with only two presenting with jaundice. Data for HCV transmission risk behaviours, including injection drug use and sexual behaviour, were not collected.[4] Overall, 20 (77%; 95% 56–91) of the participants had an SVR at 12 weeks (SVR12). Of the six participants who did not achieve SVR12, three had virological relapse, one was reinfected before post-treatment week 4, and two were lost to follow-up after achieving SVR at 4 weeks. The three participants with relapse had high baseline HCV RNA (>6·96 log10 IU/mL).

While this study[7] and other pilot studies[4,6] show promising efficacy with ultra-short duration therapy in acute HCV, many questions remain unanswered. The effect of clinical, virological, and immunological factors on efficacy—eg, HIV infection, baseline HCV RNA, method of HCV transmission (injection drug use, sexual exposure), clinical presentation, and duration of infection—remain to be adequately determined. Excellent efficacy (SVRs of 100%) has been noted in largely symptomatic, acute HCV-monoinfected patients,[6] whereas SVR was lower in Rockstroh and colleagues' study of, predominantly asymptomatic, HIV-coinfected participants. Baseline HCV RNA seems to affect response to short duration direct-acting antiviral therapy;[4,5] high baseline HCV RNA in the three relapsed cases could suggest that, even with a potent direct-acting antiviral regimen, viral suppression is protracted in individuals with a high HCV burden. It is unclear whether any people who inject drugs (PWID; a population in whom targeted therapy might prevent onward transmission) were included in the study by Rockstroh and colleagues[7] and these individuals were excluded in the study by Deterding and colleagues.[6] The effect of duration of HCV infection is also unclear. In the study by Deterding and colleagues,[6] duration of infection at screening was short (≤4 months), whereas in this study by Rockstroh and colleagues,[7] the protocol specified a duration of infection of 6 months or less. However, the estimated duration of HCV infection could not be determined for all patients, raising the possibility that treatment began in the early chronic phase of infection. Because the distinction between acute and early chronic infection is somewhat arbitrary, further research regarding timing of treatment initiation within 1 year of infection is warranted and will allow broader clinical application. Combined, these studies offer exciting potential, but are restricted by small sample sizes and selected populations.


Kateryna Kon/SPL

Moving forward, optimal direct-acting antiviral regimen choice will be crucial. Mathematical modelling has suggested that rapid on-treatment second-phase viral decline should allow shorter treatment durations.[8] The use of a potent dual-class or triple-class direct-acting antiviral regimen, including an HCV NS3/4A protease inhibitor, NS5A inhibitor, or both (with or without a nucleotide analogue) seems justified.[8] Pilot studies to date have been genotype-specific; however, a pangenotypic strategy would be ideal for clinical implementation. Further large studies of pangenotypic direct-acting antiviral therapy in well-characterised populations (including people with HIV and PWID) would greatly enhance our understanding of the use of direct-acting antiviral therapy in this field. Several studies are ongoing to assess short-duration direct-acting antiviral regimens in people with acute and recent HCV, including DAHHS-2 (NCT02600325) and REACT (NCT02625909).

Access to HCV treatment for people at high risk of onward transmission, including those with acute and recent HCV infection, should be a priority.[9] As we begin to explore the use of ultrashort direct-acting antiviral therapy in acute and recent HCV infection, one question persists: how short can we go?

Marianne Martinello, Jason Grebely, Gail V Matthews
Kirby Institute, UNSW Sydney, Sydney, NSW 2052, Australia
mmartinello@kirby.unsw.edu.au

MM reports personal fees from Abbvie outside of the submitted work. JG reports grants and personal fees from Abbvie, grants from BMS, grants and personal fees from Gilead Sciences Inc, grants and personal fees from Merck, and grants from Cepheid, outside of the submitted work. GVM reports grants and personal fees from BMS, grants and personal fees from Gilead Sciences Inc, and grants and personal fees from Janssen, outside of the submitted work.

1 Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. *Lancet HIV* 2015; **2:** e319–27.

2 Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med* 2015; **373:** 2599–607.

3 Gane EJ, Schwabe C, Hyland RH, et al. Efficacy of the combination of sofosbuvir, velpatasvir, and the NS3/4A protease inhibitor GS-9857 in treatment-naive or previously treated patients with hepatitis C virus genotype 1 or 3 infections. *Gastroenterology* 2016; **151:** 448–56.

4 Basu P, Shah NJ, John N, Aloysius M, Brown R. Poster Session 2: Hepatitis C: therapeutics (approved agents). *Hepatology* 2015; **62:** 714A–807A.

5 Martinello M, Gane E, Hellard M, et al. Sofosbuvir and ribavirin for 6 weeks is not effective among people with recent hepatitis C virus infection: The DARE-C II study. *Hepatology* 2016; **64:** 1911–21.

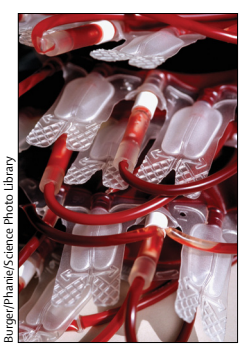
6 Deterding K, Spinner CD, Schott E, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. *Lancet Infect Dis* 2016; **17:** 215–22.

7 Rockstroh JK, Bhagani S, Hyland RH, et al. Ledipasvir–sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. *Lancet Gastroenterol Hepatol* 2017; published online Feb 27. http://dx.doi.org/10.1016/S2468-1253(17)30003-1.

8 Perelson AS, Guedj J. Modelling hepatitis C therapy–predicting effects of treatment. *Nat Rev Gastroenterol Hepatol* 2015; **12:** 437–45.

9 Hajarizadeh B, Grebely J, Martinello M, Matthews GV, Lloyd AR, Dore GJ. Hepatitis C treatment as prevention: evidence, feasibility, and challenges. *Lancet Gastroenterol Hepatol* 2016; **1:** 317–27.

Restrictive blood transfusion for gastrointestinal bleeding



Burger/Phanie/Science Photo Library

Published **Online** March 22, 2017 http://dx.doi.org/10.1016/S2468-1253(17)30077-8

See **Articles** page 354

Since 1990, global life expectancy has increased by an average 6·3 years, ranging from 3·8 to 8·3 years across continents.[1] This striking result was achieved in many fields of preventive and clinical medicine, without a dominant impact of any single measure or field. Major improvements were noted in areas such as trauma care, oncology, and cardiovascular medicine. The latter, for instance, led to the current situation in many western countries where more patients die of chronic heart failure than of acute myocardial infarction. In gastroenterology, we have seen similar improvements: in gastrointestinal oncology for instance, the median survival of patients with advanced colorectal cancer (one of the most common malignancies) strongly increased from only 6 months with best supportive care to more than 2 years with combination treatment.[2] However, such improvements were not achieved for all gastroenterological conditions. Mortality associated with gastrointestinal bleeding (the most common gastrointestinal emergency) only marginally improved. New techniques, such as endoscopic haemostasis, continuous profound acid suppression, and interventional radiology, have been introduced. At the same time, the average patient profile changed from younger adults with *Helicobacter pylori*-associated ulcers without comorbidity to elderly patients with drug-related ulcers and comorbidity. Many of these patients use combinations of drugs that synergistically increase bleeding risk, such as aspirin, NSAIDs, anticoagulants, corticosteroids, selective serotonin reuptake inhibitors, and aldosterone antagonists.[3] Their management requires a careful balance. This starts with early endoscopy with treatment of active bleeding and visible vessels, and should be combined with profound acid suppression, and red blood cell transfusion, if required.

The paper by Ayodele Odutayo and colleagues[4] in *The Lancet Gastroenterology & Hepatology* further marks the borders of this narrow path of optimal management of patients with acute upper gastrointestinal bleeding by focusing on transfusion policies. Restrictive transfusion, usually at a haemoglobin threshold of 70–80 g/L, has been studied in various other conditions, including trauma, myocardial infarction, septicaemia, stroke, and bone marrow failure. Another recent meta-analysis[5] included 31 trials with 12 587 patients with a range of conditions. Restrictive transfusion led to 43% fewer patients transfused, without affecting mortality (RR 0·97, 95% CI 0·81–1·16).[5]

The meta-analysis by Odutayo and colleagues[4] included five randomised trials with 1965 patients, comparing restrictive versus liberal transfusion for acute upper gastrointestinal bleeding. Restrictive transfusion was indeed associated with fewer transfusions, and with lower risks of rebleeding and mortality. It prevented one rebleed per 24 patients and one death per 45 patients with a bleed, although each with large confidence intervals. This finding is relevant because of the high incidence of upper gastrointestinal bleeding and its significant morbidity and mortality. The data support the existing guideline on management of non-variceal upper gastrointestinal bleeding,[6] which recommends transfusion at a haemoglobin threshold of 70 g/L.

However, this meta-analysis is limited by the paucity of original studies. Three of the five studies included were small, contributing only 7% of all patients. One of the two other studies was designed to determine the impact of restrictive transfusion.[7] The other instead aimed to assess the feasibility of a multicentre, cluster randomised trial,[8] with an unblinded design. In that