Management of metastatic pancreatic cancer: current strategies and future directions

Despite recent progress with combination regimens, pancreatic cancer remains one of the worst cancer diagnoses. Malcolm Moore reviews the current management of this disease and considers where progress may be made. Better biological understanding leading to more tailored treatments is essential, he argues, which means more phase I/II trials, and greater use of tissue sampling.

Pancreatic cancer is a significant cause of morbidity and mortality throughout the world. In Ontario, Canada, where I live and work, there are 1200 new cases and deaths each year in a population of about 12 million people. It is the fourth leading cause of cancer death in Canada, and is similarly an important cause of cancer deaths in many places around the world.

One of the challenges of treating pancreatic cancer, particularly in the use of aggressive chemotherapy, is the age distribution of those affected. As with many cancers, it has a high prevalence in the elderly. The average age of development of pancreatic cancer is over 70. Factoring the age distribution with the fact that the disease causes significant morbidity, we are dealing with a relatively frail patient population.

About 60% of patients with pancreatic cancer have metastatic disease at the time of diagnosis. The median survival in these patients is around six months. Approximately 25% of patients are diagnosed with disease

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e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues with leading European experts in the field, from controversial areas and the latest scientific developments to challenging clinical cases. One of these is selected for publication in each issue of *Cancer World*.

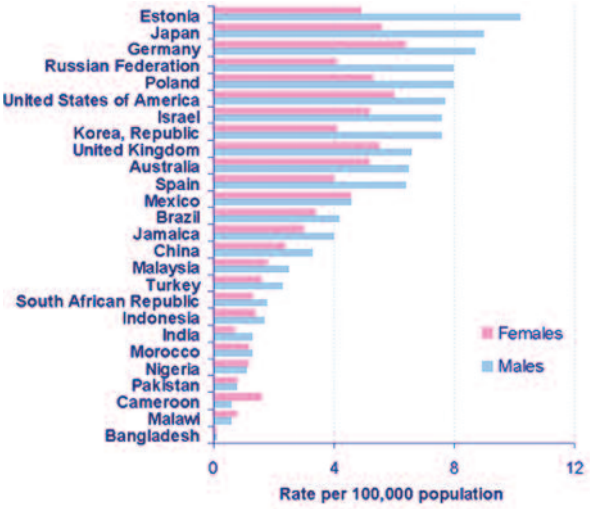
In this issue, Malcolm Moore, from the Princess Margaret Hospital, Toronto, Canada, reviews the management of metastatic pancreatic cancer, with reference to its epidemiology and biology. He considers the lessons learned so far and looks at the potential for targeted therapies and future directions for research. Jean-Luc Van Laethem, of the Erasme University Hospital, Brussels, Belgium, poses questions sent in by participants during the live webcast. The presentation is summarised by Susan Mayor.

The recorded version of this and other e-grandrounds is available at www.e-eso.net

that is localised but not resectable; we categorise these as locally advanced disease. Only about 15% of patients have resectable cancer. However, even where the cancers are resectable, median survival is still quite poor, at around 18 months, which is shorter than that of patients with metastatic colorectal cancer.

Putting all this together, 98% of patients diagnosed with pancreatic cancer will die from it within five years. To improve on this, we need better systemic therapy. Screening strategies are currently in very early stages and it is unlikely they will have a big impact within the next 10 years. We have therefore focused a lot of effort on effective systemic therapies.

MORTALITY FROM PANCREATIC CANCER



Age-standardised rates for 2002 in selected countries

Source: IARC. GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide (2002 estimates)

New drug targets for pancreatic cancer

Pancreatic cancer is not like chronic myeloid leukaemia (CML) or gastrointestinal stromal tumour (GIST), where a single molecular abnormality drives most cases. It is a very complicated cancer genetically, with several genetic abnormalities. K-RAS is often considered the 'signature' mutation in pancreatic cancer, occurring in 75%–90% of cases, but there are abnormalities in many other pathways, including Hedgehog, aurora kinase, SMAD4 and p16. All of this factors into a rather complicated malignancy.

A very interesting study in which xenografts were created from 24 resected pancreatic cancers and the genome was sequenced showed the average number of genetic mutations was 63 (*Science* 321:1801–1806). These were clustered into 12 core signalling pathways, but there was marked heterogeneity in the pathways affected, with each individual showing a different profile of genetic changes – including deletions, amplifications and mutations – in these key pathways.

KEY MOLECULAR ABNORMALITIES

Oncogene	Relevance
K-RAS	Noted in 75% to 90% of cases
Sonic Hedgehog	Crucial role in embryological signalling
AURKA (aurora kinase)	Overamplification leads to chromosomal instability
Tumour Suppressor	**Relevance**
CDKN2A/p16	Normal function induces cell cycle arrest (with Rb)
SMAD4	Encodes transcription factor; lost in 50% of cases
p53	Role in cell cycle arrest and apoptosis
Also frequently will	**see abnormalities in genes involved with**
	Wnt/notch, JNK, integrin and TGF-B signalling.
	Apoptosis
	Cell adhesion
	Invasion

This heterogeneity suggests that if we are going to solve pancreatic cancer in the distant future, we are going to be looking at combination therapy and 'personalised' therapy based on individual profiles of these genetic changes.

Trials and tribulations of chemotherapy

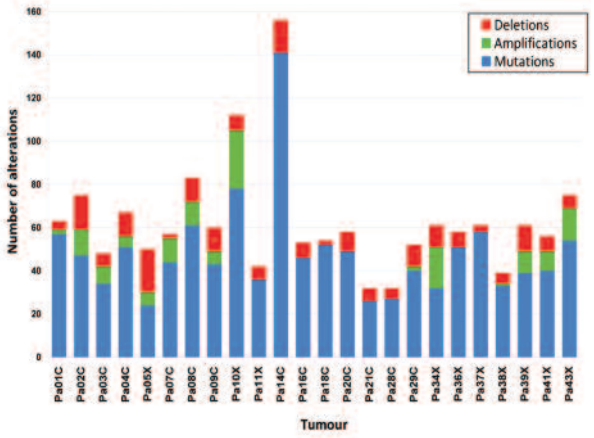
A study that I was involved in more than 10 years ago, in which gemcitabine was compared with 5-FU in metastatic pancreatic cancer, showed that, although all patients died of disease, those treated with gemcitabine had significantly better survival.

This study led to the approval of gemcitabine, the first drug approved for the treatment of pancreatic cancer. It was a relatively small study by current standards, with only 126 patients. Despite that, the results were clear, with a one-year survival of 18% with gemcitabine versus 2% with 5-FU, despite the fact that there was crossover.

Overall, the results demonstrate that gemcitabine has value in the treatment of pancreatic cancer. More patients treated with gemcitabine had stable disease and some improvements in quality of life and performance status. This was not generally associated with tumour response, which has been one of the traditional endpoints for drug trials.

Gemcitabine is now seen as a foundation for the modern treatment of pancreatic cancer. However, this study should not be interpreted as suggesting that 5-FU has no

NUMBER OF GENETIC CHANGES IN 24 PANCREATIC CANCERS



The individual biology of pancreatic cancer is very varied

Source: S Jones et al. (2008) *Science* 321:1801–1806, republished with permission from AAAS

activity. The dose and schedule of 5-FU used was probably not optimal, and it may well be that other doses have some value.

A number of relatively large phase III studies of gemcitabine with a second cytotoxic agent have been conducted in the subsequent 10 years. These include experimental drugs such as exatecan, and drugs approved for other conditions such as irinotecan, pemetrexed, capecitabine and oxaliplatin. While in some cases the phase II data showed promise, there was no improvement in survival when a secondary cytotoxic agent was added to gemcitabine.

These findings led to general pessimism about the possibility of achieving much of an improvement from combining multiple chemotherapy agents in the treatment of pancreatic cancer. However, analyses of these studies have suggested that patients with good performance status may obtain some benefit from combination chemotherapy.

Question: *Looking at the phase III studies, would you recommend a combination of gemcitabine plus a secondary cytotoxic agent, e.g. nab-paclitaxel, as an alternative to gemcitabine alone for treatment of pancreatic cancer in patients with good performance status?*
Answer: *That's an excellent question. Our practice over the last few years has been to use gemcitabine + cisplatin as an option for patients with good performance status (PS) who are interested in a more aggressive approach to treatment of their cancer, if we felt they could tolerate it. We have a community-based practice within a single healthcare system in Canada, so we see all of the patients in our centre. I would say that it is the minority of patients who could tolerate these more aggressive regimens. Anecdotally, we have had some patients who had good responses and seemed to do better.*

However, a gemcitabine + cisplatin study presented at ASCO in 2009 (Colucci et al, Abstract 4504) was a little disappointing. Not only did it fail to show a benefit, but there was no evidence of improvement even in the PS0-1 (good performance) population. This forces one to rethink whether the idea of giving more aggressive therapy to good PS patients is appropriate.

Question: *In your experience, are gemcitabine combinations well tolerated by pancreatic cancer patients?*
Answer: *We have a lot of experience with this combination, mainly because we were involved in a gemcitabine study in treatment of biliary tract cancer, which is fairly common in our area. I think tolerability really depends on the dose and schedule of gemcitabine. We found a lower dose, such as the Swiss regimen, was very well tolerated. With a higher dose, patients run into difficulty after three or four months.*

After the gemcitabine + cisplatin study presented at ASCO in 2009 showed disappointing results, many people became convinced that combination or aggressive chemotherapy probably had little role in pancreatic cancer. However, there are some data that suggest the opposite. The first is a study with gemcitabine + nab-paclitaxel (an albumin-bound paclitaxel). Paclitaxel, as far as we know, has very little efficacy against pancreatic cancer. However, the efficacy results in a phase II study conducted by Dan Von Hoff and

SURVIVAL IN RANDOMISED PHASE III TRIALS

	Gem	Gem + X	p value
Gem ± exatecan (Abou-Alfa, JCO 2006)	6.2	6.7	NS
Gem ± CPT-11 (Rocha-Lima, JCO 2006)	6.6	6.3	NS
Gem ± pemetrexed (Oettle, Ann Oncol 2006)	6.3	6.2	NS
Gem ± 5-FU bolus (Berlin, JCO 2002)	5.4	6.7	NS
Gem ± capecitabine (Herrmann, JCO 2007)	7.3	8.4	NS
Gem ± 5-FU/LV (Riess, JCO 2005)	6.2	5.9	NS
Gem ± capecitabine** (Cunningham, ECCO 2005)	6.0	7.4	NS
Gem ± cisplatin (Heinemann, JCO 2006)	6.0	7.5	NS
Gem ± oxaliplatin (Louvet, JCO 2005)	7.1	9.0	NS
Gem ± oxaliplatin (Poplin, ASCO 2006)	4.9	5.9	NS
Gem ± cisplatin (Colucci, ASCO 2009)	8.3	7.2	NS

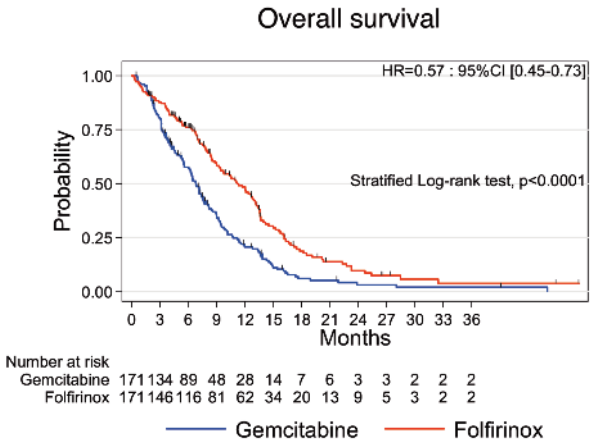
Attempts to improve outcomes from gemcitabine (Gem) by adding a second chemotherapy agent have not proved fruitful (figures indicate median overall survival, in months)

colleagues look quite encouraging (ASCO 2009, Abstract 4525). The median survival was nine months, compared to typically six months in metastatic disease. The response rate was 26% (2% complete response plus 24% partial response), as opposed to a typical response of 10% with gemcitabine. These are by no means definitive data, and it may be that these were highly selected patients. It is certainly an interesting enough result to warrant further studies, and a phase III study sponsored by Abraxis is currently ongoing.

The next study of interest was presented at ASCO three years ago by the CONKO group. It looked at the effects of a combination of oxaliplatin, 5-FU and leucovorin compared to 5-FU plus leucovorin in patients who had failed on gemcitabine, so this was a second-line population. The overall survival in the oxaliplatin–5-FU arm was 26 weeks, compared to 13 weeks in the 5-FU–leucovorin arm (Pelzer, ASCO 2008 Abstract 4508). This gives a significant improvement of three months. The study has not yet been published, but suggests that an oxaliplatin plus gemcitabine combination was not a wise choice, and combining oxaliplatin with 5-FU may be better.

A further study presented at ASCO (Reiss et al., ASCO 2009, Abstract 4006), randomised patients with advanced pancreatic cancer to systemic therapy with or without low-molecular-weight heparin. From our own experience, 25% of patients develop thromboembolic complications when they have pancreatic cancer, and many of those can be catastrophic. This study showed a significant reduction in serious thromboembolic events, but no improvement in overall survival. Having said that, the standard procedure with these patients is to use heparin, because survival tends to be short if patients have a thromboembolic problem. I think that this is something to review in the routine management of metastatic pancreatic cancer.

FOLFIRINOX VERSUS GEMCITABINE



Folfirinox (as a second-line treatment) showed a clear survival advantage over gemcitabine, but the toxicity of the combination regimen means it may not be suitable for all patients

Source: T Conroy et al. (2010) *JCO* 28:15s (abstract 4010), Published with permission

Is FOLFIRINOX the new standard of care?

This question comes out of the ACCORD11/0402 trial reported at ASCO 2010. The study has a fairly simple design and compares phase III folfirinox, which is 5-FU, leucovorin, irinotecan and oxaliplatin, with standard gemcitabine as first-line treatment for metastatic pancreatic cancer (Conroy et al., ASCO 2010, Abstract 4010).

The group had previously studied this regimen in a small group of patients (n=35) and had seen interesting activity in a good performance status population. On the basis of that, they opened a phase II/III study, and my understanding is that their intention was to go to phase III only if they saw a strong signal. They saw a 32% response rate to folfirinox and an 11% response to gemcitabine. Based on this, they continued to accrue patients into the study and expanded it as a larger phase III study. The patients who did well initially were included in the final analysis.

The regimen used was the folfox or folfiri regimen with the additional drug added in at full dose (folfox with full-dose irinotecan). This is an intensive and complex regimen, although we use folfox and folfiri very commonly in colorectal cancer and are very comfortable with these combinations.

As would be expected, the patients included were a selective population. They were young, with an average age of 61. All were of performance status 0 or 1 (almost 4% PS0 and 60% PS1), which is not the typical population for pancreatic cancer. It is important to note that the study included only good performance status patients, who could tolerate an intensive regimen.

The other unusual factor about the study population was that fewer than 40% of the tumours were in the pancreatic head, which is also not typical, as 60%–70% of cases are typically in the head. This occurred because the intention was to include

patients who had normal bilirubin, because of the drug regimen being used. Patients who had stents and did not achieve complete biliary drainage were not eligible.

In terms of adverse events, as expected there were major differences in the toxicity of the two arms. Neutropenia, febrile neutropenia, fatigue, diarrhoea and neuropathy all occurred more frequently with folfirinox. Almost half (42.5%) of patients on folfirinox also received G-CSF. Despite this difference in toxicity, the toxic death rate was low and fairly acceptable for this patient population.

The real crux of the study was a clinically and statistically significant difference in favour of folfirinox, with a partial response rate of 31% compared to 9.4% with gemcitabine, and a disease control rate of 70% versus 50%. Anecdotally, the data that were collected for gemcitabine were very typical for a patient population treated with this drug.

The median progression-free survival (PFS) values also favour folfirinox, with values of 6.4 versus 3.3 months (and highly significant *P*-values). Most importantly, the median and one-year survival values favour folfirinox: 11.1 versus 6.8 months for median survival and 48% versus 21% for one-year survival. The survival curves of the two arms demonstrate a clear separation (see opposite). We haven't seen this dramatic difference in survival with any other metastatic pancreatic study. Therefore, this is clearly an important result.

The real question and challenge for the community is: "Are there concerns about the trial methodology?" A very credible cooperative group conducted the study, and it is multicentred and randomised. There may be some concern about the fact that the patients on folfirinox generally got gemcitabine second line, while the patients on gemcitabine did not get folfirinox second line. Therefore, there is an imbalance. But while these are genuine concerns, the trial is certainly not fundamentally flawed.

Given that we've had so many negative studies of chemotherapy (this is the first one that is significantly positive), many may ask if we need a confirmatory trial to be sure it is appropriate to put patients through this very intensive regimen. There is no clear answer, but it is something that people are discussing. I think the big challenge that we will all face in our day-to-day clinical practice is that this is not a treatment for everyone. It will be difficult to distinguish between patients who are eligible for the more aggressive approach and those more suited to a palliative regimen such as gemcitabine.

The other issue, as a result of the data showing that oxaliplatin–5-FU is a successful regimen even in second-line patients, is whether it is really necessary to have all three drugs in the first-line regimen, and whether folfox with a second-line regimen would give the same results. This is, as yet, unknown.

At the end of the day, I think this is indeed a new standard for selective good performance status patients. However, most of us have not really used folfirinox in this patient population, so we will need to gain experience with it before general use in practice. There have been discussions in North America about whether we should do a phase II study of this with folfox, gemcitabine or nab-paclitaxel. This would allow us to get a sense of how patients improve and how this compares to other intensive regimens. I think this is going to be of great importance in the future.

Targeted therapy

Even with the recent folfirinox data showing improved survival, we are not going to do any better than that with more intensive chemotherapy. If we wish to improve survival beyond one year, we need to bring in targeted therapy.

Unfortunately, many of the studies so far have not been encouraging, including a study of putative RAS inhibitors with tipifarnib, a trial of gemcitabine versus the matrix metalloproteinase inhibitors marimastat and tanomastat, and a trial of EGFR antibodies with cetuximab.

The use of angiogenesis inhibitors has also been very disappointing in pancreatic cancer, with at least four negative phase III studies with different antivascular therapies including bevacizumab, axitinib and aflibercept. Sorafenib also has no efficacy. This may come back to the biology, as pancreatic cancer is not a vascular tumour, and I think there is no interest in taking these drugs any further in pancreatic cancer.

A study we did at the Canadian National Cancer Institute (NCIC) with erlotinib (an oral EGFR inhibitor) gave positive results (*JCO* 25:1960–1966), and this has now been approved for advanced metastatic pancreatic cancer. However, I think we still have some work to do on the molecular selection of appropriate patients.

This study had a simple design, randomising patients to gemcitabine plus erlotinib or placebo with no prior chemotherapy. The survival curve (see p 20) looks quite different from that for folfirinox. The median survival for the two groups was very similar because the curves come together at the end of the study. However, the overall hazard ratio was 0.81, which means a 23% improvement in average survival. The one-year survival increased from 17%

to 24% with erlotinib in this unselected patient population.

There are a couple of interesting observations from this study. First, patients who developed a rash with erlotinib had a significantly better outcome than those who did not. Patients who got a grade 2 rash had a median survival of 10.5 months and a one-year survival of 43%. Those results look very comparable to what you see with an intensive regimen such as folfirinox. The challenge has been to find out the biological significance of the data. Does it mean that everyone on the drug should have the dose escalated until they develop a rash in order to achieve a similar outcome? We do not know, and these studies are ongoing. However, the finding suggests that there is a population of patients within the overall group who do benefit.

We decided to find out whether there was a molecular method of identifying these patients. EGFR inhibitors work only in colorectal cancer patients with wild type K-RAS. Wild type K-RAS is not that common in pancreatic cancer, occurring in about 20% of cases. The hazard ratio for that population is 0.66, which shows a significant benefit with erlotinib. In the mutant population this value is 1.07, suggesting equivalence. This is an interesting observation, and further studies are being done to see if the benefit is confined to the wild type K-RAS population and is greater in this group.

Where do we go from here?

There are lots of interesting new targets that we can study in pancreatic cancer: Hedgehog pathway, Notch, heat shock protein and a number of other signalling pathways including AKT and MEK. There are drugs for most of these pathways, apart from K-RAS.

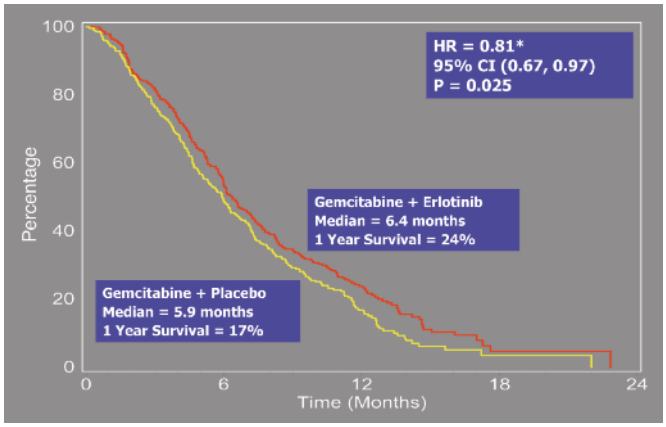
I think that it is important that we continue to look long term and realise that it is only by bringing in these types of drugs that we are going to make a major impact. The challenge over the next 10 years is to efficiently study a lot of different drugs and combinations to develop better therapy. In my opinion, we do need to focus primarily on the phase I and II arena. We also need to make sure we have uniform eligibility criteria. Trials should move on to phase III only when we get a strong signal – at least a two-month improvement in progression-free survival or survival, or a greater than 10% improvement in long-term disease control.

The other thing that we have not done so well in the past – and need to do better in future – is to incorporate biology into clinical research. It's not so bad having so many negative studies, but the issue is that we didn't collect tissue samples. If we had done this, we would know not only that the drugs were unhelpful, but also the reasons behind this. Therefore, we should be collecting tissue in all studies as a standard routine so we can try to understand what's going on at the biological level.

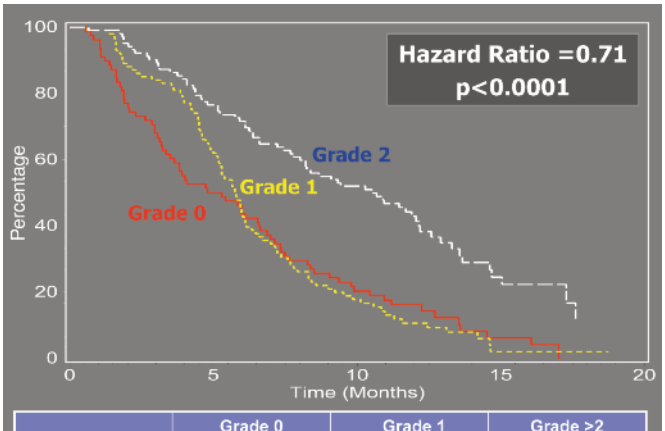
The other thing we have to start to think about is the heterogeneity of the

ERLOTINIB PLUS GEMCITABINE: OVERALL SURVIVAL

ALL PATIENTS



ACCORDING TO RASH SEVERITY

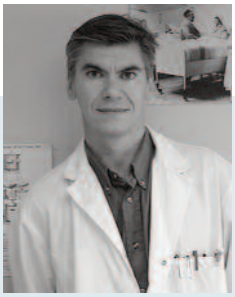


	Grade 0 N= 79	Grade 1 N= 108	Grade ≥2 N= 103
Median Survival	5.29	5.75	10.51
1 year Survival	16%	11%	43%

Adding the EGFR inhibitor erlotinib to standard therapy increased one-year survival from 17% to 24%; this figure rose to 43% for patients exhibiting a grade 2 rash

Source: MJ Moore et al. (2007) *JCO* 25:1960–1966. Published with permission

Jean-Luc Van Laethem, from Erasme University Hospital, Brussels, Belgium, hosted a question and answer session with Malcolm Moore.



Q: *Gemcitabine remains a good standard for the population, but we have to consider alternatives and possibly non-gemcitabine-based combinations, such as 5-FU–platinum in second line. We also need to find the best way to integrate folfirinox into our practice. One way to do that would be for future studies looking at gemcitabine as probably being a targeted therapy, with only about one-third of patients deriving real benefit. In the near future we may be able to select these patients based on the expression of gemcitabine nuclear transporters in tissue samples. This process is challenging in pancreatic cancer, as it is very difficult to get tumour samples. What is your feeling about targeted therapy? Do you think we should restrict erlotinib to only 20% of patients and should we rely on the chemo-evaluation? Should we make some effort to go further with this evaluation?*

A: Drawing from data in the NCIC study and my own experience, my opinion is that there is clearly a subset of patients that gets significant benefit from erlotinib – probably in the range of 10%–20%. Scientifically, it is attractive that this would be the K-RAS wild type group, because that fits with what we have learned in other diseases. However, I think the data that we generated on this in the NCIC trial is limited because we only collected tissue in about half of patients. At least two other confirmatory trials are looking at this specific question.

Anecdotally, I have a few patients in my practice who are still on erlotinib and are doing very well. We have tested them and they are all in the wild type group. Being able to identify patients who would benefit from treatment would be much more economically efficient.

Q: *What do you think about the need to overcome the RAS resistance via alternative pathways e.g. the MEK target? Do you think this process could be effective or should we investigate other pathways?*

A: We have never really had a proper RAS inhibitor. I think the next best solution would be to look at downstream pathways in RAS and target those, e.g. MEK and AKT. It is likely to involve more than one drug in order to do that effectively, because there is a lot of interaction between these pathways. If you turn off the pathway in one direction, there are other ways that the pathway can flow. Therefore, I think combination therapy is going to be the key to this problem.

Q: *Going back to systemic disease, should we consider adjuvant treatment even in resectable disease? The addition of folfirinox in this setting would be a good option to improve efficacy.*

A: I think that pancreatic cancer is clearly a systemic disease. Even among patients with resectable disease, almost all of them will recur. In many ways, we are probably asking too much of radiation therapy and if we had better systemic therapies, it is likely that we could have a more dramatic impact than with local therapy. There is no question that radiation can have an impact on a local tumour and prevent growth and progression. However, this will only be important if the overall disease can be controlled.

disease. Patients with different genetic profiles will need different approaches and we have to figure out how to incorporate this into our clinical trials. Pancreatic cancer is not a single-gene disease, and targeting single-gene pathways with single drugs is not going to be the way to make substantial progress. Therefore, we are going to have to work out how to screen multiple combinations of drugs in different patient populations. This is going to involve genetic profiling at the start of therapy.

Conclusions

It is easy to be pessimistic about metastatic pancreatic cancer, but we have made significant progress in systemic therapy. Over the past 10–15 years, one-year survival has improved from 2% to 25%. The folfirinox data show that good performance status patients can reach one-year survival rates in the range of 40%–50%. Using chemotherapy in the adjuvant setting has also improved survival and long-term disease control.

It is clear that there is a spectrum of patients, and 'one size does not fit all' in terms of treatment. Clinical judgement is important in choosing between the different therapies. However, even with new developments in treatment, pancreatic cancer is still one of the worst cancers with which to be diagnosed. We have a long way to go and need to find ways to look efficiently at all the interesting new compounds at the same time as developing the biological understanding of this cancer.