



Education & knowledge through people & facts



Mary Gospodarowicz

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Winning or losing?

ESO asks the experts

→ Franco Cavalli ■ GUEST EDITOR

Are we winning the war against cancer? This is the provocative title of the World Oncology Forum (WOF), which will take place in Lugano, Switzerland on October 25–27, to mark the 30th year of the European School of Oncology. Rather than hosting a party or a more conventional symposium, ESO feels this is the right moment to tackle some of the big questions the cancer community needs to address. Researchers, directors of cancer institutes, policy makers, chairpersons of professional and research organisations, and representatives of pharmaceutical companies, patients organisations, and international organisations such as the WHO – 80 experts in total – will gather together for two days of intense discussion. A special feature of WOF will be the participation of 20 scientific journalists who will play the role of devil's advocate, challenging the logic and the evidence for the propositions put forward.

Our understanding of the biology of cancer has improved tremendously in recent years, opening many avenues for new treatments that could work better. But how much of the progress that we seem to have achieved with targeted therapies and so-called personalised medicine is really being translated into better out-

comes, and how much is hype? What can we do about the rapidly rising number of cancer cases and deaths in low- and middle-income countries, where options for prevention, early diagnosis and treatment are so limited? Many of these countries spend only around \$50–100 per person on health every year, while the cost of the latest targeted therapies in rich countries averages \$150,000 per patient per year. Can we develop sustainable treatment options? These are some of the questions we will be debating at WOF.

Will we find answers? This is a very complex topic, which may be the main reason why last September's UN Summit on non-communicable diseases, which recognised the huge and increasing burden of cancer worldwide, failed to come up with precise commitments and deadlines. WOF will carry this discussion further, helping to sharpen the focus and the boundaries of this extremely important debate. We are proud to have the cooperation of *The Lancet*. Its editor-in-chief, Richard Horton, will lead the final session, where he will ask the conference to weigh up the arguments heard over the two days and answer the question: "Are we winning the war against cancer?" I'm sure I'm not the only one who is eagerly awaiting the verdict.

Franco Cavalli is the Chairman of the World Oncology Forum and ESO Scientific Committee

Certainly not; more potentially active drugs are available, including other taxanes and alternative platinum compounds that are probably not completely cross-resistant to cisplatin, which is most commonly used in the first-line setting. Even anthracyclines or mitomycin may show benefit in further treatment lines. To date, single-agent irinotecan, given in a biweekly (150 mg/m²) or three-weekly (250–350 mg/m²) schedule has the best evidence to improve survival and symptom control in post-progression advanced-stage gastric cancer. A smaller randomised German study of the Arbeitsgemeinschaft Internistische Onkologie (AIO) showed a consistent benefit for second-line treatment with irinotecan that resulted in a reduction of the hazard ratio for death to 0.48 (95%CI 0.25–0.92, $P=0.012$) in the irinotecan arm compared with best supportive care alone.⁷ Beyond chemotherapy, medicinal pain management, nutritional support, psycho-social support and many other interventions do not yet have proven benefit for patients with advanced gastric cancer.³

A consistent benefit of ‘salvage

chemotherapy’ has been observed in most of the prospectively defined subgroups of the Korean study.⁴ Nevertheless, in the era of personalised medicine and increasing disease stratification, the benefit of specific medicinal interventions must be challenged in future studies that may assess whether this benefit might be the same for different ethnic subgroups,⁸ for different histological phenotypes,⁹ and for different gastric cancer genotypes.¹⁰

In summary, irinotecan or docetaxel significantly prolonged overall survival compared to best supportive care in the studied patients. Second-line chemotherapy can now be considered as a proven treatment option for pretreated advanced-stage gastric cancer and this option should be integrated into a comprehensive palliative care strategy.

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Competing interests

Florian Lordick declares associations with the following companies: Pfizer, Sanofi-Aventis

Manufacturer sponsorship bias in economic analyses matters

→ David Kerr and Ahmed Elzawawy

A qualitative study indicates that there is a positive selection bias towards favourable economic analysis of targeted therapies when these are funded by the manufacturer. At a time of increasing budgetary constraints and public scrutiny of the relationship between industry and the professions, we need a more mixed economy of funding for this field.

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In terms of the history of medicine and health care, the 19th century may be regarded as the century of Public Health, clean water, sewerage and understanding the basis of infection; the 20th century might be regarded as the century of knowledge, when systematic clinical and laboratory research yielded extraordinary insights into the mechanism of disease; we predict that the 21st century will be driven by value. Considering the spiralling costs of healthcare and an often confused approach to how we define value in a societal

sense, and given the global financial crisis and the likelihood that for many nations the health budget will flat-line, it is obvious that we need more data on the relative cost-effectiveness of innovative diagnostic or therapeutic agents if we are to make transparent and defensible judgements on their relative worth. This situation is set against a backdrop of increasing suspicion from policy and lawmakers and some patient groups that the relationship between practising clinicians and purveyors of these new technologies is not at sufficient arm's length.¹ In 2007, Djulbegovic et al.,² published a fascinating historical case study of the first conflicts of interest policy at the National Academy of Sciences. A fundamental debate in this case was whether one can simply declare a financial interest or whether one must also admit that this financial interest is a potential source of bias.

Now, a new study has been published by Valachis et al.³ that addresses this question in a different way. One of the characteristic points of the study is that the authors tried to investigate the role of manufacturers' influence in various manifestations, such as the presence of any author affiliated with the manufacturer of the drug being assessed, or the presence of direct funding from the manufacturer for the health-economic study – as shown in previous studies – the role of funding and its bias in economic evaluation of drugs in oncology,⁴ and medical research in general.⁵ Of the 81 eligible studies that they identified, the authors found that economic analyses that were funded by pharmaceutical companies were more likely to report favourable qualitative cost estimates than those without an expressed funding association with these companies (28 out of 34 studies [82%]

versus 21 out of 47 studies [45%]; $P=0.003$). This phenomenon was seen to a similar degree for those studies that reported any financial relationship with the manufacturers, for example, author affiliation or author funding. Valachis et al.³ discuss the weaknesses inherent in their study with candour: the linkage between the eligible studies and their financial aspects depended solely on published details, as Valachis et al.³ made no effort to contact authors directly to further verify these data; there may have been a publication bias towards positive reports that might have skewed results; certain study criteria were poorly represented, so the database was rather small (for example, affiliation with manufacturers); and finally, their analysis was based on qualitative data. Nevertheless, Valachis et al.³ do seem to have demonstrated a consistent sponsorship bias towards the manufacturer of costly, targeted drugs with respect to economic analyses. It is concluded that the best way of dealing with perceptions of sponsorship bias is not increased rhetoric, but rather increased public funding for economic evaluation of medicines, thereby creating a true mixed economy for research funding in this field.

Does this sponsorship bias matter? If we are to adopt Michael Porter's definition of value,⁶ then, yes it does.

"Value in any field must be defined around the customer, not the supplier. Value must also be measured by outputs, not inputs. Hence it is patient health results that matter, not the volume of services delivered. But

all outcomes are achieved at some cost. Therefore, the proper objective is ... patient health outcomes relative to the total cost (inputs). Efficiency, as well as other objectives such as safety, is subsumed in the concept of value."

Adoption of any new therapeutic agent in the current climate is likely to involve trade offs, comparing the value gained from the introduction of the targeted therapy relative to existing gold standards in cancer treatment, or, even more widely, comparing its value with that gained from hip replacements or cataract operations. The latter comparison might seem absurd, but within a finite health budget in which there is no ring-fencing of cancer funding, this could become an issue. So an

economic evaluation of the new drug will have an often critical role in whether the drug is made available to cancer patients by governments or payers.⁷ If there are significant doubts about the veracity of the data, hanging over the analysis like the sword of Damocles,

then this starts to undermine the validity of the data and even reduce the chances of a targeted therapy passing over whatever health-economic hurdles have been erected in its way.

So, is there a way to square this circle? In the same way that we now have mandatory listing of clinical trials⁸ to offset publication bias, one might establish a register of pharmacoeconomic studies; approaches might be made to journal editorial boards to lower their threshold for publishing negative studies; and

"The way to deal with perceptions of sponsorship bias is not increased rhetoric, but increased public funding"

payers could establish independently funded analytical units to give an entirely unbiased view of the economic case for acceptance or not of the agent under investigation. If the workings of these analytical units were utterly transparent and open to public review, then this would further enhance their credibility and relevance to citizens. Do we think that there is some methodical misrepresentation of results? Of course not; however, the paper by Valachis et al.³ is a timely warning of the subtle biases that can creep in unnoticed, and is perhaps doubly important given the

wider economic challenges faced by all healthcare systems and, therefore, the increasing scrutiny that will be applied to all such economic analyses.

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in the battles between the Ministry of Health, pharmaceutical companies and pharmacists.

There are worries too that financial concerns are leading patients to delay visits to a doctor. "We have a problem that 15–20% of patients do not consult a physician. We compared results from 2007 to 2009, and it seems that we are seeing cancer patients at a more advanced stage than three years ago, though we do not have statistically significant data on this as yet." If true, this would mean that not only are fewer staff having to care for more patients, using fewer resources, but a higher proportion of patients are presenting with cancers that are more complex, more expensive to treat and more likely to be fatal.

While Greece is undoubtedly at the sharp end of Europe's debt crisis, it is by no means alone. With austerity the prevailing watch-

word, public spending is being reined in everywhere. Although countries such as Spain, Italy, Portugal and Ireland are in the frontline, countries such as France, Belgium, UK and the Netherlands are not far behind. Even Germany, the strongest economy in Europe, has plans to cut public sector debt by €80 bn by 2014.

As healthcare accounts for a high proportion of public spending, and cancer accounts for a sizeable chunk of healthcare spending – with its need for complex multidisciplinary approaches to care, heavy use of expensive imaging techniques, and reliance

few scrub nurses. The inevitable result is long waiting lists. Spiliotis says he just told a patient diagnosed with colorectal cancer to come back in 45 days.

Waiting times for radiotherapy are even longer, he says. In the four main cancer hospitals and nine other public hospitals with radiotherapy equipment, the waiting list is three to four months. "It is very difficult to propose neoadjuvant chemoradiation for patients with rectal cancer with waiting times like that. So the patient has to get this treatment from private practice."

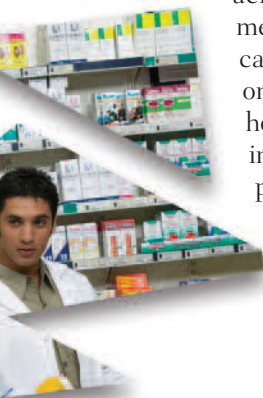
Supplies of essential cancer medicines, including Taxotere, Temodal, Avastin, Herceptin and Mabthera, are drying up, says Kathi Apostolidis, a breast cancer and patients rights advocate. She describes driving around the hospitals and pharmacies of Athens for a friend, in search of supplies of Zometa (zoledronic acid for controlling bone metastases). Pharmaceutical companies are insisting on advance payment from hospitals and public health insurance, she says, while pharmacies are refusing to deliver medicines to patients on credit. She believes patients are being held hostage

on some very expensive drugs – cancer services are under pressure as never before.

For patients, many of whom at the best of times feel they have to fight for quick access to the best treatments, the most urgent question is to what extent the financial pressures on Europe's cancer services are affecting frontline care.

In an effort to answer that question, *Cancer World* asked its European readers for feedback on how the European debt crisis is impacting on cancer care in their own countries. Ninety responses from 20 European member states suggest that there is a strong perception that the debt crisis is having a direct impact on patient care well beyond the countries facing the toughest cuts (see box *overleaf*). Drawing on comments appended to the survey and on interviews with some of the respondents reveals a patchy picture across Europe, but patterns are emerging.

ALAMY, CORBIS



WHAT THE SURVEY FOUND

A survey of *Cancer World* readers, asking about how public spending cuts are impacting on frontline cancer care, attracted 90 responses from 20 of the 27 European member states. Overall only 10% of respondents reported no impact on the quality of care cancer patients receive, with the vast majority reporting “some impact” (around 40%) or “quite an impact” (around 35%), and a little under 15% reporting “a huge impact”.

As might be expected, access to anti-cancer therapies (regardless of speed of access) showed the least impact, with almost 35% reporting no impact, a slightly higher proportion reporting “some impact” and only 25% reporting “quite an impact” or “a huge impact”. Access to other types of care, such as supportive care and rehabilitation, appears to be taking more of a hit, with only 20% reporting “no impact” and more than 40% reporting “quite an impact” or a “huge impact”.

Patients in many countries are also having to wait longer to get access to the services they need. The impact seems to be greatest for specific cancer therapies, such as surgery or radiotherapy, with almost 40% reporting a “huge impact” or “quite an impact” and only 20% reporting “no impact”. But many patients are also facing longer waiting times for seeing a specialist and getting the necessary diagnostic tests (around 25% and 30% respectively reporting the top two impact categories).

Interpretation of these findings are subject to all the usual warnings about self-selection of respondents and the subjective nature of the responses.

ACCESS TO DRUGS

Access to certain cancer drugs is changing across Europe. Fatima Cardoso, director of the Breast Cancer Unit at the Champalimaud Cancer Centre in Lisbon, reports that some drug companies have started to withhold supplies from hospitals that have been slow paying their bills. The government has been trying to intervene in cases where the hospitals have no alternatives, but Cardoso expects this problem to get worse.

Some doctors have been reduced to lying to patients because they don't want to admit there is no money to pay for the drugs they need, she says. Cardoso cites the case of a patient

whose bone metastases, which cause extreme pain and increase the risk of fracture, were being left untreated. “She had been told there are not enough data to support the use of bisphosphonates, because people are not frank enough to say: you should receive this drug but we have no money to give it to you.”

As with Greece, public cancer hospitals and oncology departments in Portugal are finding themselves flooded

with people who have had to give up private medical insurance. But even those who retain their private insurance can no longer afford the drugs they need, says Cardoso. “Even after so many years on the market, the price of trastuzumab is so shamefully high that most private health insurance barely covers the cost of one year of treatment, leaving nothing over to pay for the chemotherapy and all the other things patients need. For adjuvant therapy people sometimes do desperate things such as selling their houses to get the money for one year of treatment. But if you have to go on and on for as many years as possible, what can you do?”

In Italy, Anna Costato, who is being treated for advanced breast cancer, but is also a GIST patient advocate as a parent of a child with paediatric GIST, reports that access to new drugs takes longer and can depend heavily on where you live. This is because regional health authorities have the final say on what will be reimbursed, so a new medicine may be restricted even after approval by the European Medicines Agency and the national Italian agency AIFA.

Patients with rare cancers are hit particularly hard by measures that regulate the prescribing of drugs for off-label use. Costato believes that the measures, introduced in 2007, are now being wrongly used to restrict access to expensive drugs. She gives the examples of sorafenib (Nexavar), dasatinib (Sprycel), and nilotinib (Tasigna),



“People are not frank enough to say: you need
this drug but we have no money to give it to you”

LEVELS AND QUALITY OF STAFFING

Staff shortages and/or the de-skilling of certain roles due to budget cuts was another theme mentioned by many respondents.

In Portugal, waiting times for radiotherapy at public hospitals have been the focus of highly critical press coverage, because there are too few staff to operate facilities to full capacity. Patients are being badly let down says Cardoso. “I recently had a patient who had intensive bone metastases in her spine, particularly the cervical spine. She had been waiting for more than three months for radiotherapy. In the meantime, she developed leptomeningocarcinomatosis [affecting the tissue that covers the brain] and she is dying, at 37 years old.” Cardoso believes that while poor prioritisation of patients and poor organisation may be partly to blame, lack of personnel is also an important cause.

Costato in Italy talks of a steady decrease in the number of nurses, alongside a decrease in the number of hospital beds and length of hospital stays. What concerns her is that the care patients get on leaving hospital is largely given by low-paid untrained workers, which is impacting on the quality of care. Staff hiring is effectively frozen in hospitals, she says, which makes itself felt in longer waiting times for CT and MRI scans and for consultations with oncologists. Massimo Conio, a gastroenterologist in Sanremo, Italy, reports similar increases in waiting times for surgical procedures. Other survey respondents talk about staff shortages impacting on access to supportive therapies, “reducing the possibility of supporting the quality of life of children and families.”

Ingrid Kössler, a breast cancer patient advocate involved in Sweden’s National Cancer Control Strategy, reports similar concerns over the

increasing use of less trained nurse-assistants in place of nurses. Staffing is so tight, she says, that hospitals have come to rely on student nurses to cover absences during summer holidays. This year the student nurses are refusing to work unless they are paid a full salary; it is not clear how that will be resolved.

A scandal centred in Gothenburg over 60 patients with melanoma who were wrongly told they did not have cancer has put a spotlight on the strains personalised medicine is putting on pathology departments. Pathologists point out that they are being asked to perform many more tests for many types of patient than was the case a few years ago, and at current staffing levels they are finding it hard to cope. While Sweden is not one of the countries hardest hit by the debt crisis, says Kössler, the ageing population means that while cancer and other age-related chronic diseases are putting a greater burden on the health budget, there are now only two people working – and paying taxes – for each retired person, compared with a five-to-one ratio a few decades ago. A stagnant economy is not helping.

Comments from Ireland talk about a reduction in the number of “allied professionals” involved in the delivery of cancer care, including psychological support. A lower staff-to-patient ratio means less time spent with patients.

In the UK, survey respondents talk about reductions in follow-up visits and cutbacks in specialist breast nurses, scrubbed nurses (for operating theatres), “team members” and the administrative support necessary to free up clinical practitioners from bureaucratic functions. Nursing staff made it very clear at a recent conference that, in their experience, frontline clinical care is being directly affected by staff cuts despite assurances from the government to the contrary.



In the Netherlands staff cuts are reducing the healthcare support available to care for patients in their own homes.

Survey respondents from Spain mention longer waiting lists for diagnostic procedures and consultations with a specialist, as well as greater restrictions on access to health care from home support teams. Though it’s hard to quantify, it is clear that staffing levels are being steadily eroded through a virtual freeze on new appointments combined with the loss of many staff who were on fixed-term contracts. Cuts of 10–20% are planned for hospital staff who are not directly



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to keep the budget for care as it is now," she says. "We are told not to spend extra, but to try to be creative with what we have, so we are really evaluating the way we are reimbursing. Can we reduce the costs of reimbursement if we increase efficiency? Can we economise to have new funding to do new things?"

Greater integration is one focus point. "We pay for psychologists in cancer care, but can we also use them for other things?" Evaluating value for money is another. "Breast implants are very well reimbursed in Belgium, but they have a risk. Might it be better to use breast reconstruction with own tissue – isn't it more efficient because you have fewer complications and procedures in the longer term?" The option of adapting levels of reimbursement to encourage use of generics rather than expensive brands, where appropriate, is also under consideration.

One important spin-off of this proactive approach, says van Hoof, is that the Belgian Cancer Centre is able to back up its proposals for actions to include in the Cancer Plan with strong arguments and detailed data derived from the continuous evaluation of this plan. She believes robust cancer plans that have their own budgets and are closely monitored

and evaluated will be key to safeguarding the best quality care for cancer patients as Europe moves forward. She is glad that in Belgium they managed to get such a plan up and funded before the debt crisis struck.

But what of the countries that didn't? In Greece, John Spiliotis fully accepts that decades of virtually uncontrolled spending on healthcare, with the highest doctor-to-nurse ratio in Europe and no restrictions on prescribing, has contributed to the current crisis. He recognises the importance of a more sustainable, planned approach to delivering cancer services; he welcomes prescribing guidelines and greater use of generics; he is committed to cutting the list of lab tests, shortening the list of imaging procedures, cutting hospital stay, and using palliative rather than aggressive treatments near the end of life. He and his fellow surgeons are even shunning expensive technologies where it is safe to do so, going back to the manual procedures they haven't used for years, just to cut costs. "But we can't turn the clock back to the '60s or '70s in cancer treatments," he says. "This is a big problem

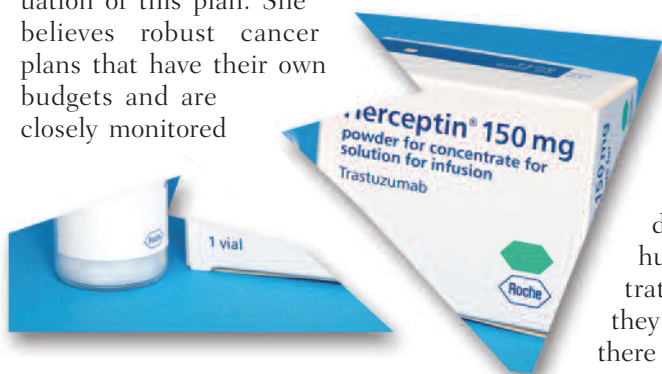
that started 30 years ago. We cannot correct it in the three to five years that Europe is demanding of us."

In Portugal, Cardoso believes there is huge scope for concentrating resources where they are most needed. "If there were proper guidance

so governments understand how to calculate overall cost-effectiveness, rather than just looking at the price of drugs, I think we could cut at least one third of the cost without affecting the quality of care," she says, "and we have to do it wisely and in a fair way." That guidance, she adds, has to come from collaboration between health economists and the people who deliver frontline care.

She is acutely aware of how much money is being wasted, for instance when vials of expensive drugs are opened, partially used, then thrown away because guidance says they can't be stored once opened. Coordinating things so that all patients receiving these drugs get them on the same day would help. However, drug companies must also cooperate in providing accurate data about the stabilisation of drugs and time-frames for use, she says.

In her own particular area, Cardoso is now focusing her efforts on advocating for all patients to be treated in breast units. "If you centralise treatment with people who know what they are doing, they will spend less," she says. She is also encouraging patient groups to speak with one voice and focus their demands on the bare essentials: access to best treatments; no cuts to medications that cannot be replaced; no cuts that affect the quantity and long-term quality of life.



"If you centralise treatment with people who know what they are doing, they will spend less"