

## Letter from the editor

### Chemotherapy-Induced Toxicity in the Community Oncology Setting: Hear No Evil, See No Evil

The annual meeting of the American Society of Clinical Oncology (ASCO) never fails to be stimulating: in a typical ASCO meeting, over 10,000 scientific papers are presented, discussing the latest results of clinical trials of new anti-cancer protocols from around the world. On leaving an ASCO meeting, one is often motivated to immediately implement the latest treatment concluded to be “the new standard of care”. In the case of metastatic disease, these newer treatments are often reported to prolong progression-free and sometimes overall survival with “manageable” toxicity.

However, enthusiasm about new treatments must be tempered by the fact that many of these new protocols were evaluated in an ideal patient population, and delivered in centres of excellence with appropriately-trained staff. Patients in a clinical trial are under close supervision and usually have access to high-quality supportive care. They are therefore able to receive higher doses of anti-cancer therapy, often for longer periods and, indeed, in these settings, any emerging toxicity is usually “manageable”. This raises the question of whether the results from such trials are fully generalisable to the community oncology setting, where patients often have more complex disease, tend to have poorer performance status than those included in clinical trials, and where facilities are not geared up to provide similar levels of supportive care.

An example from a recent study of patients with colorectal cancer highlights this important question. In 2000, the results of a large randomised trial in patients with metastatic colorectal cancer, Study 0038, were published in the *New England Journal of Medicine*.<sup>[1]</sup> A total of 683 patients were randomized to receive one of three interventions: irinotecan alone, bolus 5-FU plus leucovorin (5-FU/leucovorin), or a combination of irinotecan plus bolus 5FU/leucovorin (IFL). The trial was primarily conducted in large centres in the United States, Canada, Australia, and New Zealand. The investigators reported that IFL was associated with a median progression-free survival of 7 months compared with 4.3 months for bolus FU/leucovorin ( $P = 0.004$ ).<sup>[1]</sup> IFL was also associated with an overall survival benefit of approximately 2 months compared with 5-FU/leucovorin ( $P = 0.04$ ). The frequency of grade III/IV toxicity for adverse effects such as emesis, mucositis, neutropenia, and febrile neutropenia was reported to be lower with the IFL regimen than with bolus 5-FU/leucovorin. It was particularly interesting that the incidence of febrile neutropenia was approximately twofold higher with bolus 5-FU/leucovorin than with IFL (14.6% v 7.1%). IFL was reported to be safe with an overall incidence of treatment-related death of less than 1%. In light of these data, IFL was rightfully recognised as an important advance in the treatment of metastatic colorectal cancer.<sup>[1][2]</sup>

Within a very short time of the trial publication, reports began to emerge that IFL was more toxic than originally reported.<sup>[3]</sup> Furthermore, in the Spring 2001, two colorectal cancer studies sponsored by the National Cancer Institute that involved IFL (trial N9741 in patients with metastatic colorectal cancer, and trial C89803, which used IFL in the adjuvant setting) were interrupted because of a higher than expected early death rate.<sup>[4]</sup> A total of 10 treatment-related deaths were reported out of 289 patients given IFL (3.4%) in the N9741 trial, and 16 deaths out of 635 patients given IFL in the C89803 trial (2.5%).<sup>[4]</sup> This was in contrast to the mortality rate of 0.9% for IFL reported in Study 0038.<sup>[1]</sup> <sup>[4]</sup> The causes of death included a vascular syndrome associated with cerebral and myocardial infarctions, and a gastro-intestinal syndrome consisting of diarrhoea, nausea, vomiting, anorexia, and abdominal

cramping, which was often associated with severe dehydration, electrolyte imbalances, neutropenia, and fever.[4] The severe toxicity associated with IFL quickly led to its abandonment and replacement with the safer (and probably more efficacious) infusional 5-FU/irinotecan regimen (FOLFIRI), which fortuitously became available at about the same time.[5] [6]

Why did well-intentioned clinicians end up exposing people to what was, with the wisdom of hindsight, an unnecessarily toxic regimen? One reason is that IFL was genuinely more efficacious than 5-FU/leucovorin and, furthermore, IFL built on the widespread North American tradition of using convenient intravenous bolus regimens. Also, it inevitably took some time for North American oncologists to accept that the European-derived FOLFIRI regimen, with infusional 5-FU and irinotecan, had a therapeutic ratio that was sufficiently superior to justify the added inconvenience of an indwelling infusional device.

More importantly is the question of the discrepant toxic death rate between Study 0038, and the N9741 and C89803 trials. There are many potential explanations for the IFL experience, including chance; but here we focus on three issues which should be addressed when determining the generalisability or external validity of any trial. Study 0038 was appropriately conceived, well designed and balanced for important patient characteristics.[1] However, it primarily enrolled people with a good performance status: over 60% of participants were younger than 65 and had only one site of metastatic disease.[1] Even though there are no apparent differences in patient characteristics at baseline between Study 0038 and the National Cancer Institute studies, patients whose deaths were treatment related in the N9741 trial had a median age of 69 years. Likewise, the median age of those who died on the IFL arm of the C89803 study was 69.5 years.[4] Therefore, there is a suggestion that the risk of toxic death may be underestimated by clinical trials whose subjects are, on average, younger than the patients in the general population. In the United States, the median age for the development of primary rectal and colon cancer is 68 years and greater than 70 years, respectively [7] and, if metastatic disease occurs, it is usually detected 1 to 3 years after initial presentation. Furthermore, most patients in this greater-than-70-years age group are reputed to have four or more different chronic conditions, which increases the risks associated with intensive chemotherapy.[8] Although the average number of sites of metastases in people with disseminated colon cancer is not clear, a pooled analysis of over 20,000 participants in phase II/III studies of medical interventions for metastatic colon cancer found that less than half had only one metastatic site. As the presence of metastasis at more than one site is commonly regarded as a negative prognostic factor for colon cancer,[9] the external validity of Study 0038 could have been limited by the inclusion of more than 60% of participants with only one metastatic site.

Secondly, many of the participating hospitals in Study 0038 were centres of excellence with staff experienced in the management of toxicity-related complications. The same seems to be the case in the N9741 and C89803 trials, although the C89803 trial seems to have been conducted exclusively in North American centres affiliated with cooperative groups, whereas Study 0038 also included a few centres in Australasia, and cooperative group affiliations were apparently neither required nor stipulated in the publication. It is doubtful, however, that these distinctions were important in this case. Nevertheless, in a community setting, the level of expertise is likely to be, on average, lower than in more experienced and dedicated cancer facilities, especially those with experience in conducting trials with novel agents. By analogy it has been well established in the surgical literature that the volume of a hospital and the experience of an individual surgeon are directly related to the frequency of post-operative complications, overall hospital length of stay, and even post-operative mortality.[10] [11]

Thirdly, the comparator regimen in Study 0038, a traditional bolus 5-FU/leucovorin regimen, has itself been shown to be associated with excessive toxicity.[12] Hence, there would tend to be less contrast between the toxicity of this traditional 5FU/leucovorin regimen, and the novel IFL regimen; this might

have led to an underestimation of the real toxicity of IFL, when employed in a community setting. Therefore, a combination of younger, healthier patients under closer supervision, with drug administration in high-volume cancer centres experienced in the delivery of novel treatments — especially if the comparator regimen is quite toxic — may in general lead to an underestimate of the true toxicity risks of novel regimens, especially when applied in the community setting. Marginal regimens like IFL may only be safely delivered in large volume centres with an appropriately-trained staff. By contrast, it would be dangerous to deliver such regimens in the community oncology setting, where a substantial number of our patients receive treatment.

The case of IFL raises some important questions. Do oncologists pay enough attention to the generalisability of safety results from randomized trials that employ strict inclusion criteria when recruiting patients? Are participants in large cooperative-group trials more reflective of patients in community practice compared with other types of randomised trial? If so, do cooperative-group trials (possibly comprising less-rigorously selected participants) provide a more reliable guide to the true risks of drug-induced toxicity in people treated in the community? As a first step to answering these questions, it would be useful to know the toxicity rates in patients treated off-study in the community with bolus IFL, prior to its abandonment.

Safety data reported in meetings like ASCO are predominantly derived from clinical trials of pre-selected patients. This is especially relevant in the light of new oral targeted therapies for cancer. As a “gut” reaction, practicing clinicians would expect these new agents to be safer than intravenous chemotherapy. However, they may not necessarily be safer, and are certainly associated with their own unique toxicity profiles.[13] [14] Therefore, community oncologists should generally adopt these new therapies with caution, especially when low patient volumes do not permit an efficient ascent of the learning curve.

## The Way Forward

How can the latest new therapies that are presented at international meetings be adopted without exposing patients in the general oncology setting to unnecessary toxicity? In our opinion, the way forward consists of a two-pronged approach. Large trials need to judiciously modify their inclusion criteria to allow enrolment of more patients who are representative of people seen in the community oncology setting. Even though this may compromise the internal validity of the study (for example, a heterogeneous population makes it more difficult to balance prognostic and predictive factors evenly among the study arms, which could influence the outcomes independent of the study treatment), the trade-off would be enhanced external validity and a better understanding of how the drug would perform outside of the artificial situation created by a randomised trial. Secondly, it would be valuable to develop toxicity prediction models from patients enrolled in the original trial. These models could then be externally validated in patients outside of the original clinical trial. The value of such validated models would be their ability to identify *a priori* which patients have an elevated risk for severe toxicity.[15] [16] Such patients could be forewarned, closely monitored, pro-actively protected, and placed on an early intervention program. A Canadian group\* has recently developed a website ([www.PredictPatientEvents.com](http://www.PredictPatientEvents.com)) that features such validated risk models for various cancer related complications.[15] [17] The principle behind this website is that clinicians can enter the relevant risk factor information for a patient and then immediately receive, in “real time”, the calculated probability of the adverse event occurring.

Despite our best efforts, clinical trials have to proceed in an environment of considerable uncertainty; a combination of more open eligibility criteria and the use of validated risk models could allow us to harvest more of the upside and less of the downside. Our patients put their trust in us. Therefore, it is our responsibility to protect them.

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[www.predictpatientevents.com](http://www.predictpatientevents.com)

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