Cancer Chemo Side Effects and How to Limit Them

A Q&A with Fred Hutch physician-scientist Gary Lyman on his Nature review of acute chemotherapy-associated adverse events.

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Despite a slew of new targeted treatments and immunotherapies, chemotherapy remains a mainstay of cancer treatment. Unfortunately, so do the adverse side effects that go with systemic — or system-wide — therapies like chemo, which simply target all the fast-growing cells in your body.

Primarily, chemotherapy is meant to kill fast-dividing cancer cells, but blunt tool that it is, it also impacts normal healthy cells that also happen to divide quickly. Those include hair follicles, skin and the cells lining the gastrointestinal tract, as well as cells in the bone marrow, including immune cells. This is why cancer patients often lose their hair, experience rashes, have diarrhea and are susceptible to infections during this type of therapy.

Improvements in antiemetics over the last two decades have reduced the risk of nausea and vomiting, one of the most debilitating side effects of chemotherapy, but patients undergoing chemo can experience many others, some of which — think blood clots or severe neutropenia — can be life threatening.

Physician-scientist Dr. Gary Lyman, MD, MPH, of Fred Hutchinson Cancer Center, a longtime thought leader within the American Society of Clinical Oncology (ASCO), along with three colleagues recently published a paper in Nature Reviews Clinical Oncology offering a broad overview of common, acute chemotherapy-associated adverse events and how to manage — or better yet, prevent them.

Lyman and his co-authors cover the most common and most serious acute side effects of chemo, including febrile and severe neutropenia (serious immunosuppression and infections triggered by low neutrophils); blood clots or thromboembolisms; nausea and vomiting; diarrhea; chemotherapy-induced mucositis (mouth, throat, or gut inflammation); cutaneous reactions that affect skin, nails, tongue, eyes and scalp; and tumor lysis syndrome, an oncological emergency that occurs when a large number of cancer cells die within a short period, releasing their contents into the blood.

Curious as to what you can expect should chemotherapy be in your future? Wondering what the

future holds in the realm of new supportive measures? Read on for our Q & A with Lyman.

How did this paper come about and what are you focused on?

Dr. Nicole Kuderer [Dr. Lyman's wife and research partner] and I were invited by Nature to do this review, and we brought in two highly qualified colleagues as co-authors. This paper is focused just on the most common acute or life-threatening effects that occur during the course of chemotherapy. But there are also long-term effects, which we have not covered in this initial paper, including cancer-related fatigue, chemotherapy-induced neuropathy, cardiac injury and infertility, which a future survivorship paper will address.

We couldn't include everything so we focused on the more common side effects and the more serious toxicities. And in addition to talking about the background and how frequent and how serious these adverse effects may be, we discuss risk factors and the impact on physical and psychosocial functioning. So if a patient has a certain comorbidity or other risk factors, both clinician and patient will know that this could be a particularly concerning toxicity.

We also focused a great deal on the management of these symptoms, including what the major guidelines recommend. Both Dr. Kuderer and I have been deeply involved with guidelines on the management of these side effects over the years.

Who did you write this for? Oncologists, cancer patients, both?

We very deliberately wrote this with both clinicians and patients in mind. It's written in a technical style, but with language we hope most patients will be able to understand. And the Nature team did a very nice job enhancing our graphics.

Also, due to the overwhelming interest in this paper, the Nature editors have taken the unusual step of making the article free to download for one month [Editor's note: The article was published October 11]. This is particularly good for patient advocates and others who wouldn't normally have access. They can now get this information without a subscription or paying a premium price.

So, are most oncologists using the measures that you cover in this paper?

Most of these measures are being used in practice and most are also in the guidelines. But as we know from studies within HICOR, the Hutchinson Institute for Cancer Outcomes Research, and other research teams, clinicians often don't follow the guidelines.

We think by and large if guidelines were adhered to and these mitigation measures were used, the problems would be much less than we often see.

These recommendations are based on guidelines which are, in turn, based on a rigorous evidence review that I helped ASCO develop. However, these are just guidelines — they're not obligations or laws — and there's a great deal of variation on whether clinicians adhere to them. In some cases, they don't even know about them, but hopefully that's pretty uncommon.

Who puts out these guidelines?

ASCO is big on guidelines and I've helped lead many efforts there. There are also guidelines from the NCCN, the National Comprehensive Cancer Network, and MASCC, the Multinational Association of Supportive Care in Cancer as well as ESMO, the European Society of Medical Oncology. There are a lot of guidelines out there and there is general alignment among supportive care guidelines so you are not getting one recommendation from ASCO and one from other guidelines.

You said oncologists don't always follow guidelines? Why not?

Clinicians may not always follow the guidelines because they know the patient best. That's why they're not requirements. However, often clinicians may be too busy to keep up or they may not be up to date or as familiar with recent changes in supportive care when rapidly changing, complex therapeutic decisions occupy their minds.

The guidelines get updated every year or two with new evidence and new data. The growth in the field and the expansion of knowledge has been more rapid in recent years. There are new agents and new studies to show who should get these agents and who shouldn't. Keeping up with all of this, on top of their primary concern — the cancer itself — is a lot.

How do oncologists and patients balance the benefit and harms of chemotherapy?

Clearly, for most patients and most doctors, the first priority is whether the drug will treat the cancer, whether the cancer will respond. Side effects come second. I completely understand that and we talk about that in the literature. We feel it's all part of the same package.

Treatment is only going to work against the cancer if the patient can access it. There's a financial aspect to this. But it's also whether they can tolerate it — and tolerate the optimal dose of the treatments. It's kind of a yin-yang thing; you can't think about one without the other.

Dr. Kuderer published an important paper in Journal of Clinical Oncology with a colleague from Johns Hopkins making the point that with so many effective treatments coming along, there's often more than one option that a patient can have, with very little difference in response or survival. When that's the case, then the adverse events should take center stage. The treatment approach or the drug with fewer side effects would be the more optimal choice in that circumstance.

With ever more treatment options coming along, toxicities and adverse events are increasingly becoming the driver of the decision-making. Fortunately, a lot of patients ask questions about side effects and are looking for a more personalized approach to managing them. The patient voice in this is so important; it's why patient-reported outcomes, disability and physical and psychosocial functioning assessments need to become standard in clinical trials, guidelines and the routine care of patients with cancer.

Do the newer targeted treatments and immunotherapies have fewer side effects?

At our editor's request, we focused primarily on chemotherapy, given their broad, dose-limiting toxicities across multiple organs. However, targeted therapies and immunotherapies have their own set of side effects.

We think for many of them, the side effects are less severe or less acutely life threatening but there are exceptions, especially combinations of targeted therapies which can be potentially toxic. Dr. Kuderer is currently collaborating on a large cohort study tracking patients getting checkpoint inhibitors and capturing events and patient-reported outcomes to identify key clinical and molecular risk factors predisposing them to serious toxicities.

Therefore, many of the same issues that this paper focuses on with chemotherapy are equally important when you talk about immunotherapies or targeted therapies.

A common side effect of all cancer therapy is "financial toxicity," the negative impact of high cancer treatment costs on patients. Why do these drug prices continually escalate?

The answer is greed and lack of government oversight. Industry continues to raise prices even after a drug is FDA approved at a certain launch price. And the price continues to go up far beyond what's justified by the research cost that went into developing it or at the rate of inflation.

White blood cell boosters such as Neupogen or Neulasta that are given to cancer patients to prevent infection have recouped their cost decades ago and they still charge an arm and a leg. Fortunately, there is competition now with biosimilars and novel approaches coming along. But they're still very expensive and they're being used in combination with the latest cancer therapies, which are also extremely expensive.

Part of the blame can also be put on government and all of us for not insisting there be more regulatory control on the prices. I know there's resistance to that and it's a big political issue. Value-based pricing could bring reasonable price control, rewarding highly effective drug development rather than the limited benefit we see with many drugs.

For me, it's just mind boggling that the average citizen out there doesn't realize they're paying these companies sometimes billion-dollar profits that are being used to buy up competition, and reward leadership and investors with bonuses. In other countries, there's much closer control on prices; there's less devastation on families and patients and they actually in some cases, get better outcomes than we do here.

It's a huge issue that needs to be tackled. We need to constrain industry and make sure that the out-of-control profits that these companies are making doesn't continue to devastate patients and families, all while not discouraging innovation.

Can we expect things to change at all with the passage of the Inflation Reduction Act? Isn't CMS supposed to start negotiating drug prices with the pharmaceutical makers?

That's the hope…. Many people I have talked to are anxious about what might happen if Congress

changes its leadership and how much of what's been put into place with the Inflation Reduction Act could be undone.

I'm optimistic about this new legislation but you've got to read the fine print. It's not all drugs that will be subject to price negotiations; it's just selected drugs. The Centers for Medicare and Medicaid Services, or CMS, is taking a step in this direction. They're going to require negotiated prices for a few expensive drugs and we will see if it works well. Hopefully, it will and the program can be expanded to other drugs. Or all medications.

But the resistance and the pressure from industry is not going away any time soon. They have enormous clout and they finance many political campaigns in this country. We need to keep the pressure on, despite the promising steps forward with this recent legislation.

Anything happening with regard to new drugs to help alleviate specific side effects?

We have many new options coming down the pike; it all depends on the adverse event. With regard to neutropenia, there are some new agents coming along that look promising. One that's already on the market is a CDK4/6 inhibitor that's effective in a narrow population of small-cell lung cancer patients and may have promise in triple negative breast cancer, as well.

There's a continuous search for new agents to use in neutropenia, partly because of the enormous price of GCSF [granulocyte colony stimulating factor] treatments like Neupogen and because they don't protect everybody.

With regard to blood clots or thrombosis, there are new oral agents that seem to be just as effective as low molecular weight Heparin [an anticoagulant]. Most patients don't like doing injections every day for six months or however long to prevent a blood clot. It's much easier for patients with an oral agent, but these drugs are somewhat pricey. When you weigh in all the costs associated with getting injections and all the convenience, though, it's a step forward.

Generics have also been introduced for low molecular weight Heparin so there's some potential decrease in the cost there.

When it comes to nausea and vomiting, we have some very good drugs in this realm and we now can limit nausea and vomiting in the vast majority of patients. But it's important to use them appropriately in a risk-based approach.

That's important for the management of most chemotherapy-associated adverse events, actually. You want to assess the individual patient's risk and personalize their cancer supportive care, whether it's febrile neutropenia or thrombosis or nausea.

Speaking of precision oncology, when will we start using a patient's DNA to predict who will be more susceptible to side effects?

We've talked about this concept — pharmacogenomics — for about 20 years. There are some

areas where it’s become a consideration for certain drugs, but it’s a very narrow window. It’s not found an application across a wide swath of adverse events so it hasn’t been carefully studied.

You have to do very detailed early-phase studies and genomics on these patients and on drug levels. And there’s a big research cost associated with doing this. I have to say it’s a promise that’s still out there, but as of yet is unfulfilled across the majority of adverse events.

But it makes so much sense if we could identify a genomic profile that would tell you that this patient is at great risk for this adverse event or would likely benefit from this preventive agent or that one. Again, it’s a promise that’s yet unfulfilled with much more research needed.

Any final thoughts on the years of work that went into producing this review?

Just that I’m greatly indebted to the many outstanding mentees, professional colleagues and patients with whom I have been privileged to collaborate and from whom I have learned so much over the years. It has, indeed, been a privilege to work with so many dedicated and caring individuals striving to make cancer care and treatment safer and more effective.

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