Leveraging the potential for de-intensification in cancer care

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Abstract

Evidence-based reduction in treatment whilst preserving cancer outcomes can result in improved quality of life for patients and optimised healthcare resourcing. Using melanoma as an example, we define de-intensification and outline barriers to its implementation, and current guidance.

Comment

Improvements in the diagnosis and management of cancer have been translated into large gains in survival and reductions in treatment toxicity. The rate of drug discovery continues to increase – but there is growing concern about the disproportionate cost-benefit ratio associated with new therapies. Overall rising healthcare costs are competing within a finite resource pool, and affecting access to healthcare. Amongst higher-income countries, this is perhaps most pronounced in the United States of America, where growing political pressure and momentum has led to a series of Presidential Executive Orders and law reforms aimed at improving healthcare access and reducing the costs of prescription drugs. With this in mind, policymakers and healthcare managers are looking at how best to prioritise investment to optimise health outcomes.

The de-intensification of cancer care is an under-researched and under-implemented approach that holds substantial potential. Specifically in the management of melanoma – a cancer type that frequently involves high-cost medicines – de-intensification represents a potentially high-impact strategy with patient and economic benefits. Using melanoma as an example, we outline the concept of de-intensification in cancer, its potential benefits, barriers to its implementation, and recommendations for a path forward.

Definition and potential advantages of de-intensification

The de-intensification or de-escalation of cancer therapy can be defined as an avoidance of excess treatment whilst maintaining or improving oncological outcomes for patients. This may involve a reduction in treatment dose or duration or scheduling, or omission of a treatment phase. It may involve predictive biomarkers or decision tools for identifying individuals who are most likely to benefit from de-intensification, thereby offering a more personalised care plan. A definition and categorisation of de-intensification approaches was recently published by a subgroup of the European Society for Medical Oncology (ESMO) Precision Medicine Working Group[2]. An important addition to this framework would be individualised, values-informed decision-making around treatment options, so that the delivery of personalised oncology also becomes person-centered. For patients, de-intensification of their cancer treatment offers an opportunity to avoid some of the physical, financial, and time burdens associated with cancer care, resulting in an improved quality-of-life. Less treatment means fewer side effects, less time away from home, and reduced out-of-pocket costs. As cancer outcomes improve survivorship, issues affecting quality-of-life across various cancer types and stages have been revealed, and the significance of these endpoints for patients is becoming more evident.

Beyond this, an important secondary effect of de-intensification is the reduction of healthcare waste and, in turn, improved environmental sustainability. Estimates of the carbon footprint of healthcare range internationally from 4 to 10%[3]. In Australia, 18% of healthcare emissions are attributed to the provision and procurement of pharmaceuticals[3]. Therefore, a shortened neoadjuvant course of checkpoint inhibitor immunotherapy (CPI) rather than a longer adjuvant course in resectable stage III melanoma, for instance, could lead to a substantial decrease in resourcing requirements, including staffing, consumables, and infrastructure. An additional reduction of carbon emissions from patients' travel to and from treatment centres would also be anticipated. These secondary societal benefits of de-intensification in cancer are well-aligned with global goals to reduce carbon emissions, but, in the absence of high-quality data

supporting de-intensification from the individual patient's perspective, come with substantial ethical considerations with respect to individual versus societal benefits.

De-intensification in melanoma

In the treatment of localised melanoma, de-intensification has already moved from conceptualisation to application. Supported by robust practice-changing clinical trials, select patients with sentinel-node positive disease can safely undergo observation in lieu of completion lymph node dissection surgery[4]. Validated decision tools help clinicians to identify patients with early melanomas who are unlikely to benefit from a sentinel-node biopsy[5]. However, adopting a de-intensified approach to the systemic treatment of locally advanced and unresectable melanoma is less well established. Recently published phase 3 clinical trial data demonstrated a neoadjuvant approach of six weeks rather than a year of adjuvant CPI resulted in a longer event-free survival[6]. This is only just beginning to be integrated into standard-of-care pathways.

The two pillars of melanoma medicines – targeted therapies and CPI - are used across neoadjuvant, adjuvant and advanced settings and have had a large positive impact on recurrence and survival rates of melanoma. A proportion of CPI-treated individuals with advanced melanoma are able to achieve long-term cancer remission, and may do so even after stopping treatment early because of side effects. This raises the question of how much treatment patients really need. Is it possible to identify those who would do equally well with less therapy? These questions are particularly important to answer given the cost of these medicines and their toxicity profile. Out-of-pocket costs are largely subsidised for Australian patients covered by a universal health insurance, but, on the basis of listed prices the Australian healthcare system pays between AUD$7,000 to AUD$28,000 per month for an individual's treatment. Furthermore, although generally well-tolerated, CPIs are associated with a risk of permanent and life-changing side effects, such as thyroid dysfunction, type 1 diabetes mellitus, hypophysitis, and myocarditis, with growing recognition of the less severe chronic morbidity associated with these[7]. In this context, de-intensification and avoidance of overtreatment holds substantial potential to improve patient outcomes and efficiency of healthcare resource use.

Barriers to implementation

At present, the integration of de-intensification strategies into standard-of-care is hampered by both physician and patient factors. For the majority of patients, the fear of undertreatment and perceived increased risk of recurrence were found to be significant barriers for pursuing a less intensive approach to their cancer treatment[8]. Indeed, these negative connotations associated with "de-escalation" have led to the adoption of "de-intensification" as the preferred terminology by ESMO[2]. Patients were more likely to engage when terms such as "personalisation" and "optimisation" were used instead of de-escalation[8].

For physicians, cited reasons for reluctance to de-intensify treatment include concern about undertreatment, lack of awareness, and difficulty communicating this approach. Critically, physicians have consistently reported a lack of trial data or clinical guidance in support of de-intensification as a major barrier to implementing de-intensified modulated treatments[9]. Even when relevant data do exist, the burden of proof required for clinical implementation appears to be exceptionally high, owing to concerns from patients and clinicians about undertreatment. There may also be a potential financial disincentive associated with de-intensifying treatment for some physicians who are reimbursed through fee-for-service models – though it is difficult to estimate the extent to which this truly affects clinical practice.

Data immaturity, poor study design, and a paucity of research in this field all add to its poor evidence base, and have contributed to the slow uptake of de-intensification strategies in melanoma. Despite a plethora of research articles outlining the discovery of melanoma biomarkers – particularly gene-expression profiling – to guide treatment selection, very few candidates are progressing through to more complex and well-designed trials that could demonstrate clinical utility. A recent biomarker study that generated substantial interest reported on interferon-gamma signatures for identifying patients who would benefit from neoadjuvant CPI monotherapy rather than combination CPI[10]. The ability to avoid combination CPI in lower risk populations is particularly appealing given the high rate of immune-related adverse events associated with combination CPI. However, this biomarker-informed approach will require further validation before it can be used outside of a clinical trial setting.

Although retrospective subgroup analyses of clinical trials and cohort studies show that shorter durations of CPI – of less than 24 but more than 6 months – still result in durable treatment effects in advanced melanoma[11], uptake into clinical practice remains variable. This is unlikely to change until results are reported from the prospective clinical trials that are underway at present[12]. Similarly, clinicians have been waiting for the results of larger trials on a response-adapted neoadjuvant approach for stage III melanoma. Early phase trials showed that complete omission of surgery or adjuvant systemic therapy, as guided by an index node

response, was possible and safe[13]. The recently published phase III data support the omission of adjuvant therapy in individuals treated with neoadjuvant CPI who go on to achieve a complete or major pathologic response[6]. Tailoring patients' treatments according to their disease response creates a valuable opportunity to avoid morbid surgery and adjuvant therapy in those who are unlikely to require it. Both of these approaches represent improvements to patient selection and personalised care that have exciting implications from the perspective both of an individual's quality-of-life and of economics.

Supporting implementation of de-intensification

Improving the evidence base first requires strengthening the quality of research into de-intensification strategies and validation of these approaches. As in other areas of research, the heterogeneity of definitions of de-intensification and research design have led to challenges interpreting and synthesising the body of evidence. Recently, two papers provided guidance on how research in de-intensification should be conducted[2,14], providing a hierarchy of evidence and outlining key statistical considerations and endpoints. One of these studies laid out a roadmap, from conception to implementation, for de-intensification trials in the adjuvant setting, and prominently positioned patient engagement at the start of the research process[14]. Researchers, patients and ethics committees should engage with these guidelines, to ensure that the results of future trials are meaningful, that endpoints that matter are measured, and that research outputs can be used and contextualised within the larger body of evidence.

Beyond well designed trials, there needs to be more funding dedicated to research in this area. Given the way medicines are subsidised globally, the pharmaceutical industry has less of an incentive to fund research into de-intensification. A push for sponsorship of phase 3 trials of neoadjuvant therapy in melanoma by the pharmaceutical industry appears to be lacking, despite the potential for significant de-intensification. Therefore, it is beholden upon researchers, clinicians, and patients to advocate for de-intensification trials in appropriate cancer settings, so that funding from government and not-for-profit organisations may be allocated accordingly. Without the evidence base to support de-intensification, it will remain difficult for clinicians to transition their practice.

Fortunately, the health system has multiple stakeholders and de-intensification is not solely dependent on clinician leadership. For melanoma, there is already a historical example of system-led de-intensification, which has been driven by clinical results and cost-effectiveness. Clinical trials have shown a decreased risk of recurrence in patients treated with adjuvant CPI across stages IIIA to IIID[13]. However, much of the benefit was driven by the risk reduction in the

more advanced stages (IIIC and IIID). For that reason, Australia's drug regulatory body has effectively de-intensified adjuvant CPI for resected stage IIIA melanoma by recommending against its reimbursement, on the basis of the risk of recurrence being outweighed by the risk of harm. The Spanish Ministry of Health have accepted an even higher threshold for risk of recurrence, and do not subsidise adjuvant CPI for stages IIIA and IIIB[15]. As a result, the decision to omit CPI at the patient-level is made simpler by its financial inaccessibility.

Implementing de-intensification strategies will also require a cultural shift amongst clinicians, who will need to be supported to adjust to this emerging approach . In the past, oncology practice has tended to adopt a one-size-fits-all approach to patient care. However, advances in the understanding of cancer biology and improvements in therapeutics has prompted a transition to more personalised cancer care. To deliver the person-centred care that people deserve, it is important for clinicians to embrace more complex and time-consuming conversations to better guide patients through the nuances of evidence and communicate a de-intensified approach when appropriate. The development of decision-making tools may help to assist this transition.

Conclusion

In summary, although therapeutic advances in cancer cannot be overstated, it is important to give equal attention to the risk of overtreatment, and to recognise that more treatment does not necessarily result in better outcomes. This is becoming increasingly important as anti-cancer medicines – including immunotherapies, with their risk of life-changing adverse effects – are applied to earlier stages of cancer, and as survivorship and quality-of-life issues become more prominent. De-intensification of cancer therapies can be an effective approach to delivering person-centred care, with the potential for substantial benefits to patients, carers, and the healthcare system, and could bring secondary societal benefits by reducing carbon emissions. It should be acknowledged, however, that there are substantial barriers to adopting de-intensification strategies, with understandable physician and patient apprehension. To support the integration of de-intensification into clinical practice, the evidence base for the implementation of such approaches must be strengthened. To that end, prioritisation of research funding, improved research quality, and consistent advocacy by relevant stakeholders are essential.

Competing interests

The authors declare no competing interests.

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