

Re-evaluating adjuvant systemic therapy in cancer treatment: Scientific rigour to guide policy and practice

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ABSTRACT

The landscape of adjuvant treatment in cancer care is rapidly changing. Recent randomised trials have led to regulatory approvals for neoadjuvant and adjuvant hormonal agents, targeted therapies and immune checkpoint inhibitors. This has brought about increasing complexity in this space, challenging previously established paradigms of adjuvant treatment. As these treatments are increasingly implemented, healthcare systems around the world face the challenge of critically appraising these studies and determining whether the treatments proposed provide clinically meaningful benefit. This article considers the validity of these data in the context of fundamental principles of adjuvant therapy, as well as the scientific rigour of the relevant registration trials. We propose a greater role for practising oncologists in the regulatory and reimbursement process, using the Singaporean context as an example.

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INTRODUCTION

In the 1980s, perioperative chemotherapy succeeded in improving survival for children with osteosarcoma and validated a fundamental premise: eradication of micrometastatic disease reduces distant relapse and improves survival for a proportion of patients with solid tumours undergoing curative surgery.¹ This data was built upon preclinical insights suggesting that cytotoxic chemotherapy is more effective against the extremely low burden of disease in early solid tumours compared with macroscopic high burden metastatic disease.² Since then, the efficacy of adjuvant chemotherapy has been replicated across tumour types though the absolute magnitudes of benefit were generally modest. Today, adjuvant chemotherapy is enshrined as a curative standard of care in the treatment of many solid organ malignancies.

The advent of other modalities of systemic therapy effective in advanced disease—endocrine therapy, tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs)—provided impetus to evaluate these in the adjuvant setting. The expanding options necessitate critical reappraisal of therapeutic value in concordance with fundamental aims of adjuvant therapy and appropriate standards of scientific validity.

Adjuvant endocrine therapy

The development of adjuvant endocrine systemic therapy in breast cancer followed on from longstanding knowledge about the therapeutic value of oophorectomy in the treatment of advanced disease. Initial trials of adjuvant endocrine therapy employed ovarian radiation³ with the subsequent development of tamoxifen in the 1960s laying the foundation for the demonstration of reductions in breast cancer mortality with adjuvant tamoxifen⁴ and subsequently aromatase inhibitors.⁵ Given its lower acute and cumulative toxicities relative to cytotoxic chemotherapy, various extended durations of tamoxifen were evaluated starting in the 1970s. The demonstration of improved long-term efficacy with longer durations of therapy^{4,6} is probably contributed by the proven preventive benefit of endocrine therapy in a hormonally driven cancer;⁷ eradication of micrometastatic disease is necessarily an early process unlikely to be enhanced by protracted treatment.

Adjuvant TKI therapy

The first TKI to show overall survival (OS) benefit as adjuvant treatment for a solid tumour was imatinib for high-risk gastrointestinal stromal tumours (GIST). In the SSGXVIII/AIO study, 3 years versus (vs) 1 year of adjuvant imatinib improved 10-year relapse-free survival (RFS) (52.5% vs 41.8%) and OS (79% vs 65.3%).⁸ In this case, delaying recurrence with longer adjuvant treatment translated into OS benefit due to identical post-progression survival in both arms, which is comparable to that achieved in first-line treatment

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of advanced disease. The majority of initial GIST recurrences following imatinib discontinuation remain sensitive to salvage imatinib,⁹ likely arising from residual primary microscopic disease rather than pharmacologically-selected resistance. Additionally, the range of salvage therapies available following imatinib progression are limited. These factors also contribute to relatively uniform treatment following relapse.

The evidence in support of adjuvant TKIs in common cancers recently receiving regulatory approval is arguably more controversial. In ADAURA, 3 years of adjuvant osimertinib was compared against placebo in resected stage IB-IIIa epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC). In a preplanned analysis of OS as a secondary endpoint, 5-year OS was 88% (95% confidence interval [CI] 83–91) in the osimertinib group and 78% (95% CI 73–82) in the placebo group.¹⁰ However, only 38.5% of patients in the control arm received osimertinib upon relapse, with 56% receiving earlier-generation anti-EGFR TKIs as salvage therapy.¹¹ Osimertinib has superior efficacy compared with earlier-generation anti-EGFR TKIs and is established as the preferred standard of care in metastatic disease.¹² In the absence of mandatory crossover to provide all patients in the control arm access to osimertinib at progression, the validity of the OS benefit remains questionable since most patients in the control arm were not optimally salvaged at relapse.

In the monarchE study, evaluating women with hormone receptor-positive, human EGFR 2-negative, node-positive, high-risk early breast cancer (HR+ HER2- EBC), 4-year disease-free survival (DFS) with 2 years of adjuvant abemaciclib combined with endocrine therapy was 85.8% (95% CI 84.2–87.3) compared with 79.4% (95% CI 77.5–81.1) with endocrine therapy alone.¹³ This trial was however plagued by methodological concerns summarised by Meirson et al., including unspecified post-progression therapy in controls, inappropriate clinical endpoints and informative censoring.¹⁴ For example, imbalance in the number of early dropouts between the 2 arms without clearly specified reasons for this unequal attrition raises the possibility of dropout being related to treatment allocation and their outcomes differing. In such a scenario, sensitivity analyses reveal the already modest absolute benefit in DFS to be further diminished.¹⁴ Similar to ADAURA, the rationale for protracted therapy is also unclear, given the absence of a mechanistic basis or empirical evidence for inferior outcomes with shorter durations of treatment, as distinct from the situation in adjuvant endocrine therapy in breast

cancer and adjuvant imatinib in GIST as discussed earlier.

The well-deserved legitimacy of randomised controlled trials as the preeminent form of scientific evidence in biomedicine is predicated upon the proper interpretation of trial results, considerations for which extend beyond the completion of study accrual and achievement of a statistically positive finding. Suboptimal post-relapse therapy in controls and informative censoring can undermine the original randomisation to introduce differences between the experimental and control groups that account for observed differences in outcome. While limited techniques exist to mitigate such post-randomisation confounding (e.g. sensitivity analyses based on differing assumptions about the cause of drop-out imbalances to interrogate the possibility of informative censoring), the most crucial element may be a careful interpretation of trial results to account for the inevitable limitations of any scientific study, especially when critical decisions regarding access to treatments need to be made.

These issues of scientific validity stand above and apart from concerns regarding the toxicities and costs of protracted pharmacologic therapy. The cost-effectiveness of these adjuvant treatments have been questioned in published analyses.^{15,16} With regard to health-related quality of life, while no measurable impairment has been demonstrated with these TKIs,^{17,18} it is inescapable that non-physical forms of toxicity (e.g. time toxicity and indirect costs) will be increased in patients subjected to treatment for several years compared to those who are not. In patients with relatively more common cancers like resectable EGFR-mutated NSCLC and HR+ HER2- EBC, the cumulative costs to individuals and society will be considerable.

These concerns are brought into sharper focus by the recent LAURA study, which demonstrated a progression-free survival benefit with indefinite “adjuvant” osimertinib for unresectable stage III EGFR-mutated NSCLC following concurrent chemoradiotherapy.¹⁹ While we await OS results, an important issue to address is how this study strains, if not outright ruptures, the fundamental concept of adjuvant therapy. The aim of adjuvant treatment is to achieve a cure through disease eradication; the inescapable corollary is that it must be time-limited, because treatment should not be given for a disease that no longer exists. Indefinite treatment conforms to a suppressive therapeutic posture more consistent with early palliative therapy rather than disease eradication. If survival is eventually improved, does distinguishing adjuvant from

palliative really matter, or is it merely semantic hair-splitting? We argue the former because of the prognostic, policy and reimbursement implications of labelling a therapy curative. Evidence from chronic myeloid leukaemia (CML), the prototypical molecularly defined disease amenable to rational targeted therapy, provides a useful reference. In CML, indefinite treatment has resulted in patients achieving survival comparable to the general population.²⁰ Despite these successes, molecular and clinical cure in CML is discussed only in the context of achieving a treatment free remission.²¹ Indefinite systemic therapy is mechanistically and procedurally incompatible with a curative treatment approach.

Adjuvant ICI therapy

The transformative impact of ICI in the treatment of many malignancies has fueled multiple studies and approvals for adjuvant ICI, though many questions remain. While adjuvant ICI has demonstrated DFS benefit in stage III and high-risk stage II melanoma, OS benefit remains to be demonstrated.^{22,23} Given the long-term remissions indistinguishable from cure achieved with ICI for a fraction of patients with metastatic disease,²⁴ demonstration of OS benefit with adjuvant ICI is arguably especially critical. Mechanistically, ICIs may work best when there are sufficient tumour cells to facilitate T cell clonal expansion.²⁵ This should privilege the evaluation of neoadjuvant ICI, possibly reducing toxicity, inconvenience, cost and allowing for earlier recognition of futile therapy. To this end, the recently reported NADINA trial represents an important advance, demonstrating that 2 cycles of neoadjuvant ICI (in whom only patients with suboptimal response received further adjuvant treatment) is superior to 1 year of adjuvant ICI for macroscopic stage III melanoma.²⁶ Such evaluations should be extended to earlier melanoma stages where DFS benefit has been shown with 1 year of adjuvant ICI.

Disentangling the incremental benefit of adjuvant over neoadjuvant ICI therapy is especially challenging in the setting of resectable NSCLC. Multiple completed and ongoing trials use a variety of designs, none of which definitively establishes the most parsimonious approach to effective perioperative curative therapy with ICI. This has led to FDA approvals for neoadjuvant, adjuvant and perioperative ICI in NSCLC.²⁷ Approval was mainly based on pathological complete response rates, event-free survival or DFS, raising the recurring question around the validity of such surrogates for OS. KEYNOTE-671 is currently the only study demonstrating OS benefit with perioperative ICI

in resectable NSCLC.²⁸ In this study, neoadjuvant pembrolizumab combined with chemotherapy followed by adjuvant pembrolizumab achieved a 3-year OS of 71% (95% CI 66–76) compared with 64% (95% CI 58–69) with neoadjuvant chemotherapy alone in resectable stage II to IIIB NSCLC.²⁸ It is unfortunate that KEYNOTE-671 did not have a third arm with neoadjuvant ICI alone, to clearly define the additional value of adjuvant ICI. Clarifying this should be an urgent academic and regulatory priority, to ensure patients receive the optimal duration of perioperative ICI. Additionally, concerns about suboptimal salvage therapy in the control arm are also relevant to this study, with subsequent ICI therapy used in only 50% of the control group at time of relapse; again, this raises questions about the validity of the OS benefit reported. Indeed, a recent study confirms the likely widespread prevalence of this form of post-randomisation confounding, with only 12% of oncology studies reporting OS accounting for post-progression therapies.²⁹

In the case of another immunogenic cancer, renal cell carcinoma (RCC), 1 year of adjuvant pembrolizumab following surgery for intermediate to high-risk RCC achieved 4-year OS of 91.2% (95% CI 88.3 to 93.4) compared against 86.0% (95% CI 82.6 to 88.8) with placebo.³⁰ Once again, however, concerns of informative censoring and suboptimal exposure to ICI at salvage in the control arm have been highlighted.³¹ Furthermore, other studies evaluating adjuvant ICI in RCC patients with similar risk profiles did not demonstrate improvement in DFS or OS.³² Situating the positive results of a flawed trial within the context of multiple negative trials, the OS benefit demonstrated in KEYNOTE-564 is considerably less compelling.

The Singaporean context: Cancer drug list

In spite of these concerns around scientific and clinical validity, these adjuvant treatments have received broad regulatory approval and are included in the treatment guidelines of the leading international professional oncologic societies like American Society of Clinical Oncology and European Society of Medical Oncology. How, then, should clinicians navigate this apparent incongruity? In Singapore, the nascent health technology assessment (HTA) landscape provides a potential avenue for cancer healthcare professionals to be more involved in optimising access to high value cancer therapies. In 2022, the Ministry of Health (MOH) in Singapore introduced the cancer drug list (CDL), a curated list of cancer drugs that are approved for reimbursement through insurance

or governmental subsidies according to strictly specified indications and lines of therapy. The assessment is usually initiated by pharmaceutical companies through a company-led submission, setting in motion a comprehensive evaluation that informs the ultimate funding decisions by the MOH Drug Advisory Committee.³³ One component of this process involves engaging subspecialty cancer experts as members of a Cancer Drug Subcommittee to determine clinical appropriateness of specific therapies based on scientific and clinical evidence, independent of cost-effectiveness. Instead of relying only on subspecialty expert clinicians, we suggest that cancer physicians from a broad range of subspecialties as well as non-cancer physicians and scientists from related specialties (epidemiologists, statisticians, family physicians), be directly involved in providing the clinical expert opinion component of the HTA. This will help ensure legitimacy of evaluations in adherence to fundamental principles of biomedical evidence and cancer therapeutic principles, consistency of decisions across multiple cancer subtypes, as well as independence and sophistication of appraisals beyond statistically positive trial results. Relying only on subspecialty experts can potentially lead to scientific scrutiny of insufficient breadth and rigour, as well as possible biases accruing from vested interests in expanding subspecialty-specific therapeutic options. Increasing the breadth and depth of academic and clinician engagement in these deliberations would lend an added safeguard to the scientific legitimacy of cancer treatment access tailored to Singapore's care needs. Considering the universal value of upholding scientific rigour in assessment of medical evidence, it is plausible that such measures would also reap benefits in other healthcare systems with different HTA mechanisms at varying levels of maturity.

CONCLUSION

The modest absolute improvements in outcome accruing from most adjuvant systemic treatment confirms that the majority of patients will have their outcome (relapse or cure) unimpacted by such therapy—adjuvant treatment necessarily subjects all patients to the toxicity and inconvenience of treatment so that only a fraction will derive benefit. Novel adjuvant therapies purporting to provide meaningful therapeutic value should thus meet the very highest standards of scientific and clinical validity, especially since such treatments are accorded a high degree of legitimacy and priority

as part of a curative treatment approach. If and when they fall short, such shortcomings should be acknowledged and access to such therapies appropriately constrained. To this end, the emerging mechanism of HTA in Singapore provides oncologists and other cancer physicians a chance to play a more substantive role in ensuring that access to adjuvant systemic therapy is optimised for the benefit of patients and society.

Ultimately, what is our role as oncologists? Are we advocates and guides for individual patients or guardians of finite public goods that need to be rationed? We venture the answer to be both, though the undoubted occasional tension between these 2 roles needs to be navigated judiciously. Perhaps we can assert what our role should not be—uncritical dispensers of pharmacologic agents at the whim of regulators, industry and individuals. The fear is that we are caught in the vortex of a positive feedback loop, with low levels of trust between patients and physicians diminishing the legitimacy of clinical interactions in favour of guidelines and regulatory approvals, leading to more automatic and less nuanced guideline abidance at the bedside, diminishing trust even further. It is time for cancer physicians as a community to short-circuit this self-defeating loop through active participation in local regulatory and reimbursement processes as part of our effort to ensure cancer patients receive the highest quality of treatment available.

Ethics

Not applicable.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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