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Immunogenic cell death inducers and PD-1 blockade as neoadjuvant therapy for rectal cancer

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ABSTRACT

Immuno-oncological cancer management is shifting to neoadjuvant treatments. In patients with gastrointestinal cancers, particularly locally advanced rectal cancer, neoadjuvant chemoimmunotherapy often induce complete responses, hence avoiding surgical intervention. Recent clinical trials indicate that combinations of oxaliplatin-based chemotherapy and PD-1/PD-L1-targeting immunotherapy can be safely administered before surgery with curative intent.

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Total neoadjuvant therapy (TNT) is an evolving approach for the treatment of certain malignancies, including locally advanced rectal cancer (LARC), where neoadjuvant chemotherapy and/or radiation therapy is administered before surgery rather than in an interspersed manner where some treatment is given before and some after surgery (Figure 1a–d). Thus, TNT aims at maximizing the benefits of neoadjuvant therapy by delivering a comprehensive course of treatment prior to surgical resection of the tumor. The integration of PD-1-targeted immune checkpoint blockade into TNT offers the chance to additionally (re-)activate anticancer immunity, hence increasing the likelihood of complete tumor eradication and reducing the risk of metastasis.

Recently, Zhang Z et al.[1] presented results from a phase II trial of immunotherapy-based TNT (iTNT) for proficient mismatch repair or microsatellite stable (pMMR/MSS) LARC (Clinical Trial Information, NCT04518280-TORCH). In this study, the complete response rates (CR rate, 54.2% ~ 56.5%) were significantly higher as compared with conventional neoadjuvant chemoradiotherapy, or some studies involving similar agents but not TNT (CR rate 39.8% ~ 44.8%), indicating that iTNT was profoundly more efficient even in tumors with limited immune infiltrate prior to treatment. Indeed, pMMR/MSS LARC is immunologically relatively cold and refractory to neoadjuvant PD-1 blockade (without chemotherapy) compared to deficient mismatch repair or microsatellite stable (dMMR/MSI) LARC. Of note, three components in the iTNT regimen, namely oxaliplatin, fluorouracil (the active metabolite of capecitabine), as well as X-ray irradiation, have been well described for their ability to induce immunogenic cell death (ICD) that can sensitize tumors to PD-1 blockade, the final component of the iTNT regimen.[2–4]

ICD is a specific form of cellular demise that elicits adaptive immune responses against dead-cell antigens and establishes durable immunological memory.[3,4] In addition to their known direct anti-proliferative effects on cancer cells, *bona fide* ICD inducers are endowed with the ability to remodel immunosurveillance, as demonstrated by their capability to induce anticancer vaccination effects in immunocompetent mouse models.[3] ICD-inducing chemotherapies trigger a pre-mortem stress response in malignant cells, such as endoplasmic reticulum (ER) stress and autophagy, prompting the release of immunostimulatory signals known as danger-associated molecular patterns (DAMPs) that can be sensed by a panel of pattern recognition receptors (PRRs) expressed on dendritic cells (DCs) (Figure 1e). Mechanistically, premortem autophagy occurring in the context of ICD facilitates the release of adenosine triphosphate (ATP) from cancer cells.[5] Extracellular ATP (eATP) binds to the purinergic receptors P2Y2 (P2RY2) and P2×7(P2RX7) on DCs, thus acting as a chemoattractant, guiding inflammatory DCs to the tumor site, activating the NLRP3/ASC/caspase-1 inflammasome, and promoting interleukin-1 beta (IL1β) secretion required for interferon-gamma (IFNγ) -producing $CD8^+$ T cell polarization.[3] Evidence from infection models indicates that the activation of P2RX7 by eATP is also essential for the establishment, maintenance, and functionality of long-lived central and tissue-resident memory $CD8^+$ T cell populations.[6] Once recruited into the

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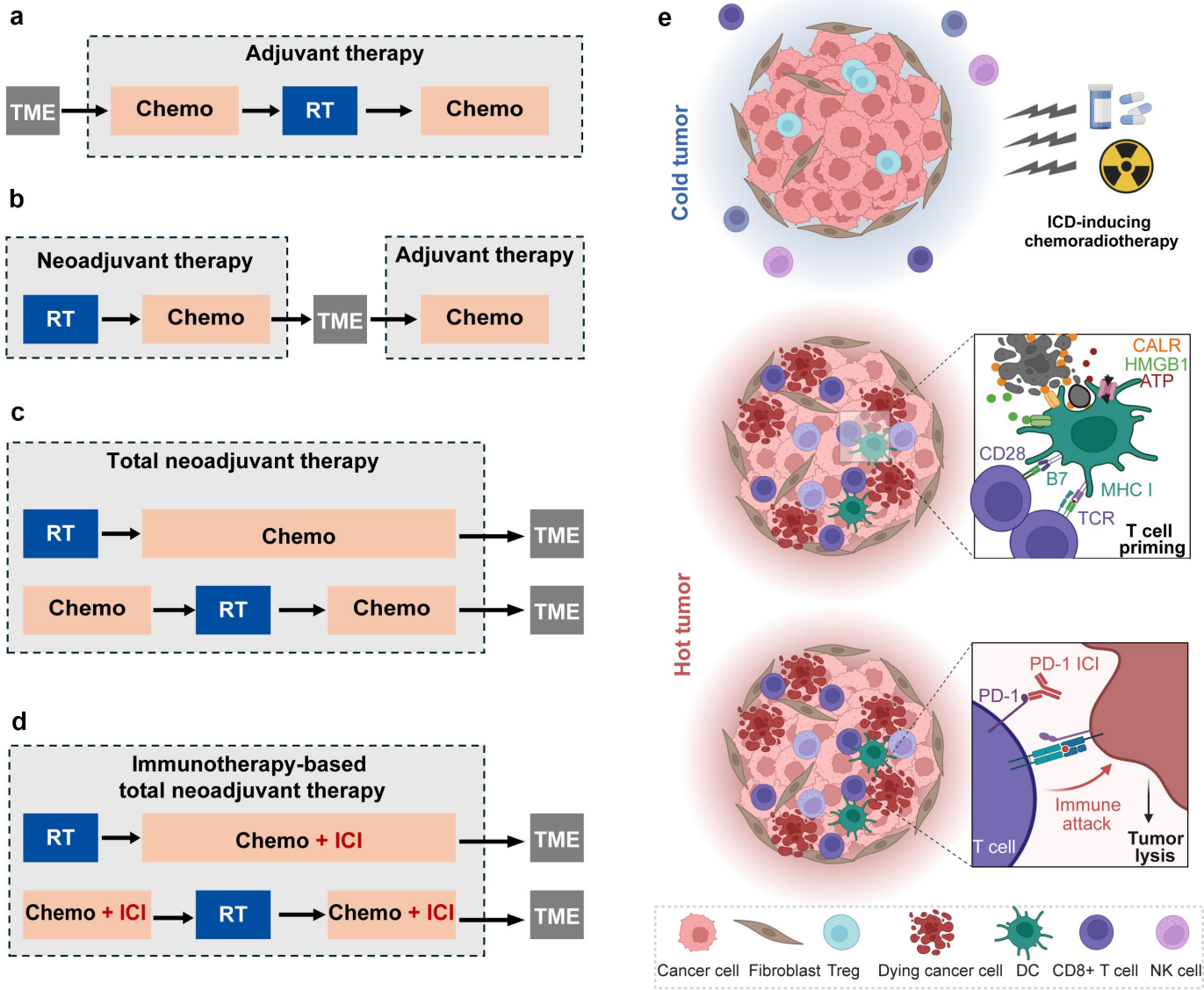

Figure 1. A brief overview of the evolution of therapeutic strategies for locally advanced rectal cancer, emphasizing the role of immunogenic cell death mechanisms. Radiation and chemotherapy can be administered as adjuvant therapy (a), neoadjuvant therapy and adjuvant therapy (b), or total neoadjuvant therapy (c), depending on risk factors and patient responses. Induction and consolidation immunotherapy sequences are combined with chemotherapy to enhance treatment outcomes (d). Tumors subjected to ICD-inducing chemoradiotherapy release a distinct array of damage-associated molecular patterns (DAMPs) that are detected by pattern recognition receptors (PRRs) on DCs. This process recruits immature DCs to the tumor microenvironment, where they engage with dying cancer cells and uptake TAAs to activate T cell-mediated adaptive immune responses. As a result, immunologically "cold" tumors–characterized by a lack of CTLs and NK cells, alongside an abundance of immunosuppressive Tregs–can be transformed into "hot" tumors, marked by CTL and NK cell infiltration and reduced Treg activity. Additionally, exhausted CTLs can be further revitalized with ICIs to enhance tumor lysis (e). ATP, adenosine triphosphate; CALR, calreticulin; Chemo, chemotherapy; CTL, cytotoxic T lymphocytes; DC, dendritic cells; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; RT, radiotherapy; TAA, tumor-associated antigens; TME, total mesorectal excision surgery; Treg, regulatory T cells.

tumor bed, DCs are primed through formyl peptide receptor 1 (FPR1), which engages with annexin A1 (ANXA1) released from dying cancer cells, thereby luring DCs into their close proximity.[3] Premortem ER stress occurring in the context of ICD facilitates the translocation of calreticulin (CALR) from the ER lumen (its usual location) to the surface of the plasma membrane, where it serves as an "eat-me" signal acting on CD91 receptors expressed on DCs, thereby stimulating the phagocytosis of cancer cell corpses.[3] Moreover, the surface-exposed CALR binds to NKp46, thus facilitating cancer cell killing by NK cells.[7] ICD is also characterized by the release of high mobility group box 1 protein B1 (HMGB1) from the nucleus into the extracellular milieu when the plasma membrane becomes permeabilized. HMGB1 interacts with Toll-like receptor 4 (TLR4) expressed on DCs to stimulate their maturation and cross-presentation of tumor-associated antigens to naïve T cells.[3] ICD inducers also prompt rapid type I interferon (IFN) production by malignant cells via the activation of a TLR3- or STING-elicited signal transduction cascade. Type I IFNs establish autocrine and paracrine circuitries that ultimately result in the release of chemokine (C-X-C motif) ligand 10 (CXCL10), mediating chemotactic and immunostimulatory effects on T lymphocytes.[3]

In summary, ICD stimulates DCs to present tumor antigens to T cells, leading to their activation and clonal expansion. This process generates CTLs that specifically target and destroy residual cancer cells, effectively converting immunologically cold into hot tumors (Figure 1e). Importantly, the combination

of ICD induction with PD-1 checkpoint blockade has shown synergistic effects in numerous studies, leading to enhanced tumor regression and prolonged survival in animal models and gastric cancer patients.[2] In the study by Zhang Z et al.,[1] patients with pMMR/MSS LARC received neoadjuvant treatment with ICD inducers including oxaliplatin, capecitabine, and radiotherapy, in combination with PD-1 blockade (Figure 1d). This iTNT regimen elicited a substantially higher CR rate (50%) than those observed in prior studies involving chemoradiotherapy with the same agents, though without immunotherapy[8–10] (Figure 1c). Of note, a substantial fraction of patients treated with iTNT (25% corresponding to 30 out of 121 evaluable patients) did not undergo any surgery and remained disease-free, indicating the possibility of organ preservation via a non-operative management. Hence, the study by Zhang et al.,[1] provides clinical evidence for the synergistic effects of ICD inducers and immunotherapy against LARC.

It is important to mention that not all chemotherapeutic agents are able to induce ICD. Contrasting with oxaliplatin, which is a strong ICD inducer, cisplatin is a poor ICD inducer.[2–4] Accordingly, comparisons of two randomized phase III clinical trials targeting unresectable gastric and gastro-esophageal junction carcinomas apparently validate this observation.[2] Thus, oxaliplatin-based chemotherapy favorably interacted with PD-1 blockade, while cisplatin-based chemotherapy failed to be improved by concomitant PD-1 blockade.[2] For this reason, it appears crucial to use the adequate (ICD-inducing) platinum-containing drug when designing clinical trials. Similarly, regulatory bodies such as the FDA and EMA, which have approved combination therapies involving PD-1 blockade with "platinum-based chemotherapy" (which include carboplatin, cisplatin, and oxaliplatin), should be aware of the importance of avoiding vague recommendations and rather narrowly define chemotherapeutic agents in chemoimmunotherapeutic combination regimens.

Disclosure statement

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Data availability statement

All data that led to the conclusions in this manuscript have been referenced and all sources have been described.

Author contributions

YW and LZ collected data, designed display items and edited the manuscript. ZZ and PL wrote the manuscript.

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