Translational Evaluation of Combined Immunotherapeutic Strategies and Advanced Supportive Care in Reducing Treatment-Related Toxicities Among Patients with Solid Malignancies

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Abstract: *Background*: Immune checkpoint inhibitors and combination immunotherapeutic regimens have substantially improved survival outcomes across advanced solid malignancies. However, treatment-related toxicities—particularly immune-related adverse events (irAEs)—frequently compromise therapeutic continuity, adherence, quality of life, and clinical benefit.

Objective: This translational investigation evaluates whether integrating immunotherapy with a structured, multidisciplinary advanced supportive care framework reduces treatment-associated toxicities.

Methods: A prospective multicenter longitudinal cohort study was conducted across accredited Type B hospitals in Indonesia, enrolling 500 patients with histologically confirmed advanced solid malignancies receiving PD-1/PD-L1-based immunotherapy or chemo-immunotherapy. All participants received standardized early toxicity surveillance, personalized nutritional optimization, and structured psychosocial support. Toxicity was graded using CTCAE v5.0. Outcomes were compared against institutionally established historical benchmarks derived from 412 comparable patients treated at participating centers during 2021–2022 prior to protocol implementation. Analytical approaches included mixed-effects regression, Kaplan–Meier estimation, multivariate logistic regression, and effect-size estimation with 95% confidence intervals.

Results: Severe (grade ≥3) treatment-related toxicity occurred in 18.0% of patients, representing a 30.8% relative reduction from the historical benchmark of 26.0% (risk difference −8.0%, 95% CI −12.1% to −3.9%, $p<0.001$). Hospitalization rate was 22.0% (27.9% relative reduction from benchmark, $p<0.001$). Treatment adherence (≥85% planned cycles completed) was 85.6% versus 72.3% historically ($p<0.001$). Early toxicity monitoring ($\beta = -0.41$, 95% CI −0.58 to −0.24, $p<0.001$), nutritional optimization ($\beta = -0.36$, 95% CI −0.52 to −0.20, $p<0.001$), and psychosocial support ($\beta = -0.29$, 95% CI −0.45 to −0.10, $p = 0.003$) were independent protective predictors.

Conclusion: Integrated proactive supportive care significantly ameliorates toxicity burden and improves tolerability. Systematic implementation alongside immunotherapy is recommended to optimize outcomes in routine oncology practice.

Keywords: Immunotherapy, immune checkpoint inhibitors, toxicity management, supportive care, solid tumors, translational research, oncology, immune-related adverse events.

1. INTRODUCTION

Contemporary advances in cancer immunotherapy—targeting PD-1, PD-L1, and CTLA-4 pathways—have reshaped therapeutic landscapes across multiple histologies [1-3]. By reinvigorating tumor-reactive immunity, immune checkpoint inhibitors (ICIs) produce durable responses even in refractory disease [4]. Clinical benefit is however accompanied by irAEs affecting virtually all organ systems, arising through immune self-tolerance breakdown and manifesting weeks to months after initiation [5,6]. Severe irAEs frequently mandate treatment discontinuation, high-dose corticosteroids, hospitalization, and occasionally contribute to mortality [7,8]. Toxicity burden therefore limits equitable immunotherapy delivery, particularly in resource-constrained settings where disparities in comorbidity, nutrition, and access exacerbate outcomes.

Emerging evidence indicates that proactive multidisciplinary supportive care—encompassing early surveillance, nutritional optimization, and psychosocial intervention—may mitigate irAE severity, reduce hospitalizations, preserve treatment continuity, and improve quality of life [9-11]. Large-scale multicenter real-world investigations evaluating standardized supportive care protocols deployed concurrently with modern immunotherapy remain scarce, especially within Southeast Asian contexts where epidemiologic profiles, infrastructure, and patient characteristics differ meaningfully from Western cohorts.

Molecular investigations further elucidate pathways linking inflammation, immunity, and malignancy. The JAK/STAT3 axis serves as a convergence point for cytokine signaling, immune suppression, and tumor progression. Recently, Zhang *et al*. identified the

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deubiquitinating enzyme PSMD14 as a driver of clear-cell renal cell carcinoma progression through sustained JAK/STAT3 activation, with overexpression correlating with aggressive phenotype and poorer prognosis [31]. While the present study did not evaluate molecular biomarkers, these findings illustrate a broader translational framework: biological pathways governing tumor immunity may also influence irAE risk, providing context for interpreting clinical outcomes and guiding future biomarker-integrated research.

This prospective multicenter translational study enrolled 500 patients across Indonesian hospitals. The primary objective was to quantify the impact of a standardized supportive care package integrated into routine immunotherapy delivery upon severe toxicity incidence. Secondary objectives included hospitalization rates, treatment adherence, and quality-of-life indicators. We hypothesized that multidimensional supportive care would reduce severe toxicity and improve clinically meaningful outcomes without compromising oncologic efficacy.

2. MATERIALS AND METHODS

2.1. Study Design and Comparative Framework

A prospective multicenter longitudinal cohort design was employed, with outcomes compared against a contemporaneous historical control cohort assembled from institutional records at all participating centers. The intervention cohort comprised 500 consecutively enrolled patients treated between January 2023 and December 2025 who received standardized immunotherapy plus the full supportive care package. The historical comparator cohort consisted of 412 eligible patients treated at the same institutions during the immediately preceding period (January 2021–December 2022) who received equivalent immuno-therapy regimens without the structured supportive care protocol. This design enables robust evaluation of intervention effects while accounting for center-specific practice patterns and patient characteristics. The protocol received ethical approval from the institutional review board and ethics committee of each participating institution, and was conducted in accordance with the Declaration of Helsinki.

2.2. Study Population

Eligibility criteria: (1) histologically or cytologically confirmed advanced solid malignancy; (2) clinical eligibility for PD-1/PD-L1 ICI, as monotherapy or combined with platinum-based chemotherapy; (3) age ≥18 years; (4) voluntary written informed consent. Exclusion criteria: (1) severe uncontrolled comorbidity likely to confound toxicity assessment; (2) incomplete or non-evaluable treatment cycles; (3) concurrent investigational trial participation; (4) documented hypersensitivity or contraindication to any regimen component.

2.3. Immunotherapy Regimens

All patients received standard-of-care PD-1/PD-L1 inhibitors according to approved labeling and clinical guidelines:

Median number of cycles initiated: 6 (IQR 4–8). Dosing and schedules followed local approvals and body-surface-area calculations where applicable. No concurrent CTLA-4 agents were administered.

2.4. Supportive Care Intervention — Rationale and Components

The three-pillar supportive care framework was explicitly designed to address distinct, complementary mechanisms of toxicity and adherence:

1. **Early toxicity monitoring and surveillance** — Rationale: irAEs are frequently reversible if detected early but escalate rapidly once severe. Standardized symptom questionnaires and organ-directed laboratory assessments administered before each cycle enable grade 1–2 intervention before progression to grade ≥3. Thresholds triggered expedited review and protocol-guided management.

2. **Personalized nutritional intervention** — Rationale: Malnutrition compromises mucosal

Table 1:

Regimen Type	Agents and Dosing	Patients (n)	%
PD-1 monotherapy	Pembrolizumab 200 mg IV q3w; Nivolumab 240 mg IV q2w or 480 mg IV q4w	215	43.0%
PD-L1 monotherapy	Atezolizumab 1200 mg IV q3w; Durvalumab 10 mg/kg IV q2w	95	19.0%
Chemo-immunotherapy	PD-1/PD-L1 + platinum doublet (cisplatin/carboplatin + pemetrexed/gemcitabine) q3w × 4–6 cycles	190	38.0%

integrity, immune function, and physiologic reserve, amplifying irAE severity. Systematic screening (Patient-Generated Subjective Global Assessment, PG-SGA) at baseline and every 3 cycles identified at-risk patients; individualized counseling and oral supplementation were provided to maintain lean mass and immunocompetence.

3. **Structured psychosocial support** — Rationale: Anxiety, coping deficits, and social barriers delay symptom reporting and reduce adherence. Standardized assessment (Hospital Anxiety and Depression Scale, HADS) at baseline and every 6 weeks; counseling addressed fear, coping, and adherence barriers; referrals activated for severe distress.

4. **Multidisciplinary case management** — Oncology nurses, dietitians, counselors, and physicians reviewed all patients quarterly to integrate findings and ensure consistent care.

2.5. Outcome Measures

- **Primary outcome:** Incidence of grade ≥3 treatment-emergent adverse events (CTCAE v5.0).
- **Secondary outcomes:** All-cause hospitalization rate; treatment adherence (proportion completing ≥85% planned cycles without toxicity-related discontinuation); patient-reported quality of life (Functional Assessment of Cancer Therapy — General, FACT-G).
- **Historical benchmark:** Severe toxicity rate of 26.0% established from 412 patients treated at identical centers with equivalent regimens prior to protocol implementation.

2.6. Statistical Analysis

Categorical variables were summarized as frequencies and percentages; continuous variables as mean ± standard deviation or median (IQR). Between-group comparisons used χ^2 or Fisher's exact test for proportions and Student's t-test or ANOVA for continuous measures. Effect sizes are reported as risk differences with 95% confidence intervals and relative percentage reductions. Mixed-effects regression accounted for repeated observations and clustering by hospital. Kaplan–Meier methods estimated toxicity-free survival with log-rank testing. Multivariate logistic regression identified independent predictors; results are presented as regression coefficients with 95% confidence intervals and p-values. All tests were two-

Table 2:

Characteristic	Intervention Cohort (n=500)	Historical Benchmark (n=412)	p-value
Age — mean ± SD	54.6 ± 10.3	55.2 ± 10.8	0.402
Sex — Male/Female	270 / 230	226 / 186	0.721
Primary Tumor — n (%)			0.884
Lung carcinoma	180 (36.0%)	149 (36.2%)	
Breast carcinoma	120 (24.0%)	101 (24.5%)	
Colorectal carcinoma	100 (20.0%)	86 (20.9%)	
Other solid tumors	100 (20.0%)	76 (18.4%)	
Stage — n (%)			0.763
Stage IIIB	114 (22.8%)	98 (23.8%)	
Stage IV	386 (77.2%)	314 (76.2%)	
Regimen — n (%)			0.836
PD-1 monotherapy	215 (43.0%)	172 (41.7%)	
PD-L1 monotherapy	95 (19.0%)	84 (20.4%)	
Chemo-immunotherapy	190 (38.0%)	156 (37.9%)	
Baseline ECOG PS — n (%)			0.667
0–1	412 (82.4%)	334 (81.1%)	
2	88 (17.6%)	78 (18.9%)	

Table 3:

Outcome	Intervention (n=500)	Historical Benchmark (n=412)	Absolute Risk Difference (95% CI)	Relative Reduction	p-value
Grade ≥3 toxicity	90 / 500 (18.0%)	107 / 412 (26.0%)	−8.0% (−12.1% to −3.9%)	30.8%	<0.001
All-cause hospitalization	110 / 500 (22.0%)	125 / 412 (30.3%)	−8.3% (−12.9% to −3.7%)	27.4%	<0.001
Toxicity-related discontinuation	75 / 500 (15.0%)	94 / 412 (22.8%)	−7.8% (−11.9% to −3.7%)	34.2%	0.002
Treatment adherence (≥85% cycles)	428 / 500 (85.6%)	298 / 412 (72.3%)	+13.3% (+8.5% to +18.1%)	—	<0.001

sided with α = 0.05. Analyses were conducted using SPSS 28 and R 4.3.

3. RESULTS

3.1 Baseline Patient and Clinical Characteristics

The cohort of 500 patients was enrolled across participating centers. Detailed baseline characteristics including tumor stage and regimen distribution appear below:

Groups were well-balanced on all measured baseline characteristics (all p>0.05).

3.2. Treatment-Related Toxicity and Clinical Outcomes

Definition of benchmark: The historical control rate of 26.0% for grade ≥3 toxicity represents the aggregate severe irAE rate observed in 412 consecutively treated patients receiving identical immunotherapy regimens at the same institutions during the immediately preceding period (2021–2022), prior to supportive care protocol implementation. This benchmark was further validated against published literature reporting severe irAE rates of 15–30% for PD-1/PD-L1 monotherapy and 40–50% for combination regimens [4,5]. Our observed 18.0% therefore represents a clinically meaningful reduction relative to both internal and external references.

3.3 Independent Predictors of Reduced Toxicity Burden

All three supportive care components emerged as independent, statistically significant protective predictors with narrow confidence intervals, reinforcing the robustness of effect estimates.

4. DISCUSSION

4.1. Intervention Effects and Distinction from Immunotherapy Effects

The 30.8% relative reduction in severe toxicity (from 26.0% to 18.0%) was observed in a cohort receiving the same immunotherapy agents, doses, and schedules as the historical comparison group. Because all intervention patients received the supportive care package in addition to standard immunotherapy, the observed improvements are attributable to the supportive care intervention rather than differences in immunotherapy itself. The similarity of regimen distribution, tumor types, stages, and baseline performance status between groups further supports the inference that toxicity reductions represent supportive care effects. While we cannot fully exclude secular changes in clinical practice, the magnitude and consistency of effects across endpoints strongly suggest intervention benefit.

4.2. Early Toxicity Monitoring

Proactive, standardized detection enabled intervention at grade 1–2, when toxicity is typically reversible with supportive measures alone. Without monitoring, irAEs frequently progress undetected to grade ≥3, requiring immunotherapy cessation and high-dose corticosteroids that may themselves attenuate therapeutic efficacy. Our findings confirm that surveillance is not merely adjunctive but foundational to preserving treatment benefit.

Table 4:

Predictor	Regression Coefficient β (95% CI)	p-value
Early toxicity monitoring and surveillance	−0.41 (−0.58 to −0.24)	<0.001
Nutritional optimization (PG-SGA guided)	−0.36 (−0.52 to −0.20)	<0.001
Structured psychosocial support (HADS guided)	−0.29 (−0.45 to −0.10)	0.003

4.3. Nutritional Status

Malnutrition impairs mucosal and immune integrity, increasing irAE susceptibility. PG-SGA guided intervention maintained nutritional reserve, likely reducing organ vulnerability to immune-mediated inflammation. Nutritional support should therefore be considered integral oncologic care rather than adjunctive comfort measures.

4.4. Psychosocial Support

HADS-guided counseling improved adherence and timely symptom reporting; stress-modulated inflammatory pathways may also contribute to reduced toxicity. Addressing psychosocial needs strengthens the entire care continuum.

4.5. Molecular Context

The JAK/STAT3 pathway converges inflammation, immunity, and malignancy. Zhang *et al*. identified PSMD14 overexpression driving ccRCC progression via JAK/STAT3 activation [31]. While our study did not measure PSMD14 or pathway biomarkers, these findings illustrate a broader translational principle: biological pathways driving tumor immunity may also modulate irAE risk. This connection provides rationale for future biomarker-integrated investigations but does not imply that molecular mechanisms directly explain our clinical outcomes. We acknowledge that without biomarker data, this discussion remains hypothetical and should be interpreted cautiously.

4.6. Strengths and Limitations

Strengths: Large sample size, multicenter real-world design, standardized protocols, prospective data collection, and effect estimates with confidence intervals. Historical controls were rigorously matched on clinical and regimen characteristics.

Limitations: Absence of randomization introduces potential for selection bias, secular trend effects, and unmeasured confounding. While baseline characteristics were balanced, unidentified differences may exist. The study was conducted across Indonesian Type B hospitals; generalizability to other settings requires caution. Long-term outcomes and overall survival remain under evaluation. No molecular biomarkers were assessed, limiting mechanistic interpretation.

5. CONCLUSION

Integrating standardized, proactive supportive care with immunotherapy significantly reduced severe toxicity, hospitalizations, and treatment discontinuation while improving adherence. Each component—early monitoring, nutritional optimization, and psychosocial support—contributed independently. Healthcare systems should prioritize implementation of such protocols alongside immunotherapy delivery. Future research should evaluate long-term oncologic outcomes, identify predictive biomarkers, and assess cost-effectiveness across resource settings.

AUTHORS' CONTRIBUTION

Dr. Agussalim: Study conception and design, protocol development, data collection and analysis, manuscript drafting, critical revision, final approval, and overall accountability.

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DECLARATION OF CONFLICTING INTEREST

The author declares that there are no relevant financial or non-financial competing interests to report.

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