Table 2 Hormone refractory biochemical progression-free survival according to each clinicopathological parameter

Univariate and multivariate analyses for hormone refractory biochemical-progression free survival rates

Parameter		Hormone refractory biochemical progression-fee survival rates		Univariate analysis			Multiivariate analyses		
		5 years	10 years	HR†	95% CI††	*p*	HR†	95% CI††	*p*
Age, years (median 67.0)	<65	94.6	89.9						
	≥65	94.1	87.6			0.687			
PSA, mg/ml [median 15.1 (3.5–160.7)]	<10	97.1	97.1	1					
	10-20<	88.9	80.8	6.18	1.1, 116.8	0.043			
	20-50<	100.0	100.0	0.0	0,.	0.315			
	≥50	90.9	60.6	12.9	1.9, 254.0	0.008			
Clinical stage	T1,2	100.0, 100.0	100.0, 88.9	1			1		
	T3~4	90.0	84.8	7.47	1.4, 137.1	0.013*	3.65	0.7, 68.6	0.161
Gleason score at biopsy	5~7	98.5	98.3	1			1		
	≥8	86.8	70.3	8.38	2.2, 55.0	0.001*	4.73	1.2, 31.7	0.027*
Seminal vesicle invasion	−	98.4	98.4	1			1		
	+	88.1	73.1	7.42	1.9, 48.7	0.003*	4.53	1.1, 30.1	0.030*
Surgical margin	−	100.0	100.0						
	+	93.6	86.7			0.183			
Microlymphatic invasion	−	97.2	95.0	1			1		
	+	87.9	74.4	5.33	1.5, 24.7	0.006*	2.18	0.9, 12.8	0.140
Microvascular invasion	−	96.3	90.5						
	+	92.2	85.6			0.468			
Perineural invasion	−	100.0	100.0						
	+	93.6	86.7			0.242			
Gleason score at prostatectomy	5–7	95.7	89.6						
	≥8	91.4	71.4			0.114			

†Hazard ratio by Cox proportional-hazard models
††Confidence interval

patients with pT2-3 N0-1 prostate cancer, including 61% of T3 and 16% of N1 patients [14]. Although longer observation periods are awaited, they reported 5-year biochemical progression-free and overall survival rates of 92.5 and 95.5%, respectively, in patients treated with adjuvant hormonal therapy consisting of goserelin and bicalutamide, after a median observation period of 4.4 years. Some studies reported encouraging results in more challenging patients with more severe pathological stages. Spahn et al. reported on 173 patients with pT3N0-1 tumors, including 43.3% of N1, who had undergone prostatectomy [15]. They reported an 8-year cancer-specific survival rate of 86.3% and an overall survival rate of 77.3% after a median observation period of 5.7 years in patients treated with adjuvant hormonal therapy comprising an LHRH analog with or without flutamide. Siddiqui et al. reported an advantage of adjuvant hormonal therapy with an LHRH analog, bilateral orchiectomy, or anti-androgens in a retrospective study of 191 pT3bN0M0 prostate cancer patients [9]. They found that, although the overall survival rate was similar to that in the matched control cohort, the biochemical progression-free and cancer specific survival rates were improved, with 10-year biochemical progression-free and cancer-specific survival rates of 60 and 94%, respectively, after a median follow-up of 10 years [9]. In accordance with this previous report, subgroup analyses of pT3bN0 patients in the current study demonstrated excellent outcomes, with 5- and 10-year cancer-specific survival rates of 95.1 and 90.8%, respectively. These results indicate that the combination of radical prostatectomy and adjuvant androgen deprivation therapy may produce excellent outcomes in patients with pT3N0M0 prostate cancer.

The current study achieved a 10-year cancer-specific survival rate of 96.3% and a 10-year estimated overall survival rate of 85.7% after a median follow-up period of 8.2 years. These survival rates were higher than those in previous reports, which may require an explanation. Immediate commencement of adjuvant androgen deprivation therapy after radical prostatectomy, and its comparatively long duration (at least 5 years), may have contributed to the beneficial effect. Supportive treatment strategies, such as prompt adjustment or alteration of hormonal therapy

in the event of a slight increase in PSA levels, may also have improved the treatment efficacy. It is also possible that Japanese men are more sensitive than other ethnic groups to hormonal therapy after radical prostatectomy. Akaza et al. reported 5- and 10-year cancer-specific survival rates of 90 and 69%, respectively, in 68 Japanese patients with clinical T3N0M0 tumors who were treated with hormonal therapy alone [16]. However, Ueno et al. reported 5- and 8-year progression-free survival rates of 59.8 and 48.1%, respectively, in 245 Japanese patients with clinical T3N0M0 cancers treated with combined androgen blockade (63.5%) or castration [17].

The Asia Consensus Statement 2013 in the NCCN Clinical Practice Guidelines in Prostate Cancer states that androgen deprivation is a candidate treatment option for post-radical prostatectomy recurrence in Asian patients negative for distant metastasis. The results of the current study suggest that a treatment strategy consisting of radical prostatectomy and immediate adjuvant androgen deprivation therapy may offer favorable cancer control in Japanese patients with pT3N0M0 prostate cancer. This strategy was also feasible and well tolerated. Immediate adjuvant androgen deprivation therapy thus represents an attractive option for patients with pT3N0M0 prostate cancer.

Few studies have reported on prognostic factors in patients with pT3 prostate cancer. The current study found that higher clinical stage, higher Gleason score at biopsy, and seminal vesicle and microlymphatic invasion were unfavorable factors, and multivariate analyses identified seminal vesicle invasion and Gleason score at biopsy as independent prognostic factors for hormone-refractory biochemical progression. Interestingly, no patients with clinical T1 tumors (n = 20), negative surgical margin (n = 12), or negative perineural invasion (n = 11) experienced hormone-refractory biochemical progression. In partial agreement with our results, previous studies identified Gleason score, PSA, seminal vesicle invasion and lymphovascular invasion as prognostic predictors in patients with pT3N0 stage prostate cancer undergoing radical prostatectomy [10-13].

The limitations of this study included its retrospective nature and the relatively small sample size. Further investigations, including prospective studies, are needed to compare the additive effects of multimodal therapies in patients with pT3N0, to allow the better selection of patient populations most likely to benefit from treatment. The current study indicated a significant hazard ratio for seminal vesicle invasion or with higher Gleason score at biopsy, suggesting that patients with pT3b or with higher Gleason score may be the leading candidates for such studies.

These findings were based on pathologic results. The majority of the patients included in the study were considered to have lower grade and stage at diagnosis, and T3N0 was only diagnosed after radical prostatectomy. These results suggest that radical prostatectomy is a reasonable option for the initial treatment of prostate cancer, and allow for the better selection of patients who will require additional therapies.

Conclusions

Radical prostatectomy with immediate adjuvant androgen deprivation therapy may be a valid treatment option for patients with pT3N0 prostate cancer.

Competing interests

The authors declared that they have no competing interests.

Authors' contributions

YTS made substantial contributions to conception and design, analysis and interpretation of data and was involved in drafting the manuscript. HF made substantial contributions to conception and design, analysis and interpretation of data and was involved in revising it critically for important intellectual content. MS, TF, TN and HN made substantial contributions to acquisition of data. HK made substantial contributions to conception and design and helped to draft the manuscript. TM and MF evaluated the pathological specimens in a manner blinded to the clinical information. YH conceived and supervised the study, helped to draft the manuscript and was involved in revising it critically for important intellectual content. All authors read and approved the final manuscript.

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UROLOGY - ORIGINAL PAPER

Risk factors for septic shock in acute obstructive pyelonephritis requiring emergency drainage of the upper urinary tract

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Abstract
Purpose To assess the risk factors for septic shock in patients with acute obstructive pyelonephritis requiring emergency drainage of the upper urinary tract.
Methods We retrospectively reviewed the records of 48 patients who underwent emergency drainage of the upper urinary tract for sepsis associated with acute obstructive pyelonephritis at our institute. Univariate and multivariate analyses were performed to identify the risk factors.
Results Among 54 events of sepsis, we identified 20 events of septic shock requiring vasopressor therapy. Cases with shock were more likely than those without shock to have ureteral stone (70 vs 38 %, $p = 0.024$) and positive blood culture results (81 vs 28 %, $p = 0.006$). They received drainage significantly earlier than those without shock (1.0 vs 3.5 days, $p < 0.001$). Univariate analysis demonstrated that acute obstructive pyelonephritis by ureteral stone, rapid progression (the occurrence of symptoms to drainage $\leq$1 day), positive blood culture, leukocytopenia (<4,000/mm^3), thrombocytopenia (<120,000/mm^3), and prothrombin time international normalized ratio $\geq$1.20 were correlated with septic shock. Multivariate logistic regression analysis identified thrombocytopenia ($p = 0.005$) and positive blood culture ($p = 0.040$) as independent risk factors for septic shock.
Conclusions Thrombocytopenia and positive blood culture were independent risk factors for septic shock in acute obstructive pyelonephritis requiring emergency drainage. Thrombocytopenia would be practically useful as a predictor of septic shock.

Keywords Acute obstructive pyelonephritis · Septic shock · Thrombocytopenia · Ureteral drainage

Introduction

Acute obstructive pyelonephritis sometimes requires emergency drainages of the upper urinary tract by percutaneous nephrostomy or retrograde ureteral stenting [1]; however, septic shock may develop despite appropriate emergency drainage.

The Surviving Sepsis Campaign Guidelines, first published in 2004 and updated in 2008 [2, 3], are now regarded as the international standard for treatment of severe sepsis including urosepsis. Although the guidelines recommend emergency drainage for acute obstructive pyelonephritis, little information is known for the risk for developing septic shock in spite of drainage. Recently, Yamamoto et al. reported that age and presence of paralysis were independent risk factors for septic shock in patients receiving emergency drainage for acute pyelonephritis with ureteral calculi. However, in this study, they analyzed limited cases only with ureteral calculi [4], and for cases with other causes, the risk factor remains uncertain. Thus, in this study, we have attempted to identify the risk factors for septic shock in cases with other causes as well as ureteral calculi.

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Methods

We retrospectively reviewed the records of patients who underwent emergency drainage of the upper urinary tract for sepsis associated with acute obstructive pyelonephritis at our institute from April 2006 to September 2011. The diagnosis of sepsis was made by the criteria for systemic inflammatory response syndrome (SIRS), which included two or more of the following conditions: (1) body temperature greater than 38 °C or less than 36 °C, (2) heart rate greater than 90 beats per minute, (3) tachypnea, as manifested by a respiratory rate greater than 20 breaths per minute or hyperventilation, as indicated by a partial CO_2 pressure less than 32 mmHg, and (4) white blood cell count greater than 12,000/mm^3 or less than 4,000/mm^3, or more than 10 % immature neutrophils [5, 6]. Patients' age, sex, underlying comorbidities, performance status, the side of infected kidney, type of drainage, cause of obstruction, and the time interval between the occurrence of symptoms of pyelonephritis and drainage were recorded. We also evaluated SIRS score, the results of blood and urine culture before antibiotic treatment, and laboratory examinations including blood leukocyte count, blood thrombocyte count at nadir, C-reactive protein (CRP), serum creatinine and total bilirubin level, and prothrombin time international normalized ratio (PT-INR) prior to drainage.

Septic shock was defined as sepsis with a systolic blood pressure less than 90 mmHg despite adequate fluid replacement or using vasopressors for at least 1 h [7, 8]. By comparing patients who did or did not progress to septic shock, we identified risk factors for septic shock.

Chi-square test, Student's t test, and Mann–Whitney U test were used for univariate analysis to compare variables between cases with septic shock and without. All variables that were significant on univariate analysis were entered into multivariate analysis, and logistic regression analysis was used for multivariate analysis. Analyses were performed by JMP 9 (SAS institute Inc., Tokyo, Japan). P values less than 0.05 were considered significant. This study was approved by the institutional ethical committee (3,124).

Results

We identified 48 patients who met SIRS criteria and required emergency ureteral drainage for acute obstructive pyelonephritis. A total of 54 emergency drainage procedures were undertaken, with once in 44, twice in two, and three times in two patients. The patients' clinical characteristics are shown in Table 1. The cause of obstruction was ureteral stone in 27, malignant neoplasm in 14, obstruction of ureteral stent in six, anastomotic stenosis of ileal conduit in three, adhesion after lower abdominal operation in two, ureteropelvic obstruction in one, and unknown in one. The patients' laboratory data prior to drainage is shown in Table 2. Culture samples prior to treatment were taken from blood and urine in 34 events (63 %) and 53 events (99 %), respectively. Organisms isolated from blood and/or urine culture were *Escherichia coli* ($n = 22$), *Pseudomonas aeruginosa* ($n = 5$), and other gram-negative bacilli ($n = 12$).

Septic shock occurred in 20 events of drainage. No patients without septic shock died, but one female 74-year-old patient died of septic shock in 8 days after drainage. She had end-stage bladder cancer and poor performance status but no other complications. The other 19 cases with septic shock finally recovered from septic shock with intensive care and the median length of hospital stay was 15 days (5–75). Patients with septic shock were treated with antibiotics, vasopressors in all cases, blood infusion in 10 cases, gamma globulin in 10 cases, antithrombin III agents in 6 cases, blood purification therapy in 4 cases, and recombinant human soluble thrombomodulin in 3 cases (Table 3).

Cases with shock were more likely than those without shock to have ureteral stone ($p = 0.024$) and positive blood culture results ($p = 0.006$). They received emergency drainage significantly earlier than those without shock ($p < 0.001$).

Univariate analysis demonstrated that septic shock was significantly associated with ureteral stone ($p = 0.024$), rapid progression (the occurrence of symptoms to drainage $\leq$1 day, $p = 0.01$), positive blood culture ($p = 0.006$), leukocytopenia (<4,000/mm^3) ($p = 0.01$), thrombocytopenia (<120,000/mm^3) ($p < 0.001$), and coagulopathy (PT-INR $\geq$ 1.20) prior to drainage ($p = 0.004$). Multivariate logistic regression analysis identified thrombocytopenia [odds ratio (OR) 23.90; 95 % CI 2.64–216.18; $p = 0.005$] and positive blood culture [OR 9.11; 95 % CI 1.11–74.79; $p = 0.040$] as independent risk factors for septic shock.

Discussion

We have found that thrombocytopenia and positive blood culture were significantly associated with septic shock independently in acute obstructive pyelonephritis requiring emergency ureteral drainage.

Previous studies documented coagulopathy and thrombocytopenia as the predictors of progression of sepsis [9, 10]. This would be natural in considering the process of multiple organ dysfunction and septic shock [9–11]. Septic conditions stimulate the release of local and systemic proinflammatory mediators, which would result in low systemic vascular resistance and hypotension [12, 13].

Table 1 Characteristics of patients

	Septic shock (+) ($n = 20$)	Septic shock (−) ($n = 34$)	p value
Sex			
Male	5	11	0.568†
Female	15	23	
Age			
Mean (range)	60 (40–81)[a]	64 (38–84)[a]	0.200‡
Underlying comorbidities			
Diabetes mellitus	5	10	0.972†
Malignancy	5	16	0.188†
Steroid use	3	7	0.883†
Laterality			
Right	12	19	0.768†
Left	8	15	
Performance status			
0	13	20	0.157†
1	4	8	
2	1	6	
3	2	0	
Drainage			
Percutaneous nephrostomy	5	15	0.160†
Retrograde ureteral stent	15	19	
Cause of obstruction			
Urinary stone	14	13	0.024†
Others	6	21	
SIRS score			
2	4	11	0.388†
3	8	15	
4	8	8	
Interval between onset and drainage (days)			
Median (range)	1.0 (0–3)[b]	3.5 (0–20)[b]	<0.001‖
≤1 day	13	7	0.001†
≥2 days	7	27	

[a] Mean (range), † chi-square test, ‡ Student's t test, [b] Median (range), ‖ Mann–Whitney U test

These mediators also activate coagulation cascade and promote fibrin clot formation and platelet activation, inducing coagulopathy and thrombocytopenia [12–14]. Our univariate analysis also demonstrated that thrombocytopenia and prolonged PT-INR were risk factors, although the latter did not remain as a significant factor in multivariate analysis. Thrombocytopenia may be clinically useful as a predictor of septic shock, since blood platelet count is a quick test.

Positive blood culture was marginally associated with septic shock in our study. Hsu et al. [15] reported that patients with complicated acute pyelonephritis with positive blood culture were likely to present severe sepsis or shock. However, the results of blood culture need at least 8 h, which may weaken the utility of blood culture in emergency situation [16, 17]. Moreover, in our study, blood culture was not taken correctly in 20 patients; in 14 cases, antibiotic therapy had been already begun before the referral to our institute, which might lead potential selection bias because these cases might have been under serious condition.

Yamamoto et al. reported that the interval from the occurrence of symptoms to drainage was significantly shorter in patients with septic shock in univariate analysis [14], which is similar to our results. Thus, the rapid progression may be an important risk factor but multivariate analysis in our study failed to show the significance.

Serum creatinine and bilirubin were not significant factors in our study, although they are included in the sequential organ failure assessment score [18], which was commonly used to evaluate the organ damage or predict outcomes in septic patients [18, 19]. This may be because serum creatinine level in patients with acute obstructive pyelonephritis, sometimes elevated by obstructive uropathy

Table 2 Laboratory data of patients prior to drainage

	Septic shock (+) ($n = 20$)	Septic shock (−) ($n = 34$)	p value
White blood cell count (/μL)	11,200 (1,200–47,900)[a]	11,650 (4,000–35,200)[a]	<0.001[†]
Leukocytopenia (<4,000/μL %)	5	0	0.01[‡]
Thrombocyte count nadir (×10,000/μL)	8.15 (0.80–41.90)[a]	22.0 (6.6–54.9)[a]	<0.001[†]
Thrombocytopenia (<1.2 × 10^5/μL %)	16	3	<0.001[‡]
PT-INR	1.31 (0.92–3.51)[a]	1.13 (0.90–1.49)[a]	0.005[†]
Elongation of PT-INR (≥1.20 %)	16	12	0.004[‡]
CRP (mg/dL)	13.69 (4.33–29.74)[a]	12.84 (0.88–37.68)[a]	0.425[†]
Serum creatinine level (mg/dL)	2.26 (0.93–6.50)[a]	2.13 (0.45–19.79)[a]	0.802[†]
Serum total bilirubin level (mg/dL)	0.80 (0.20–1.70)[a]	0.60 (0.20–2.40)[a]	0.914[†]
Blood culture			
Positive	13	5	0.006[‡]
Negative	3	13	
Urine culture			
Positive	19	23	0.064[‡]
Negative	1	10	

[a] Median (range), [†] Mann–Whitney U test, [‡] chi-square test

Table 3 Risk factors for septic shock

Variables	Number	Multivariate analysis	
		OR (95 %CI)	p value
Cause of obstruction			
Ureteral stone	27	Reference	0.951
Other	27	1.81 (0.13–23.75)	
Blood culture			
Positive	16	Reference	0.040
Negative	18	9.11 (1.11–74.79)	
Leukocytopenia (<4,000/μL)			
No	49	Reference	0.999
Yes	5	>50 (0.00 to >200.0)	
Thrombocytopenia (<1.2 × 10^5/μL)			
No	35	Reference	0.005
Yes	19	23.90 (2.64–216.18)	
PT-INR			
<1.20	26	Reference	0.266
≥1.20	28	3.24 (0.41–25.75)	
Onset to drainage			
≥2 days	34	3.25 (0.37–28.65)	0.288
≤1 day	20	Reference	

rather than SIRS, may not reflect the severity of sepsis. Serum bilirubin level was elevated in only 5 patients with shock in our study.

Comorbidities such as malignancy, diabetes mellitus, and steroid use were known to be associated with infectious diseases [20], although they were not necessarily risk factors for septic shock in acute obstructive pyelonephritis. Yoshimura et al. [21] reported that diabetes mellitus and immune suppression status were not associated with septic shock by examining 473 patients with urosepsis associated with upper urinary tract calculi. Similarly, Lee et al. [22] found that diabetes mellitus and malignancy were not

related to septic shock in 208 bacteremic acute pyelonephritis patients. However, the reason for the lack of association was not discussed in these papers.

The weakness of our study is a retrospective analysis of a single institution with a limited number of cases. Confirmatory studies with a larger population may be required.

Conclusion

Our study revealed thrombocytopenia would be clinically more useful as a predictor of septic shock in the emergency room.

Conflict of interest None declared.

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Guest editorial: immunotherapy for hematological malignancies: the quest to overcome tolerogenic drive

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How easily a healthy body can defend itself against ordinary pathogens! If only it was possible to do the same against self-derived malignancies. Unfortunately, however, the physiology of the immune system discourages such a persistent fight by establishing the overwhelming hurdle of "tolerance". For this reason, tumor immunotherapy stands as an ultimate challenge to the fundamental basis of immunology. Will we ever win this battle? Recent remarkable advances in related fields are finally beginning to make tumor immunologists confident enough to answer in the affirmative.

In fact, it has been hematologists who have led the field of tumor immunotherapy through their work in allogeneic hematopoietic stem cell transplantation, which exploits the power of graft-versus-tumor effects. However, this is inevitably accompanied by graft-versus-host disease, which precludes elderly patients, who represent a major population suffering from hematological malignancies, from receiving allogeneic transplantation. Clearly, we must develop novel therapies for such patients.

In contrast to the tremendous power of allogeneic reaction, autologous antitumor responses are usually feeble. Heightening them to a clinically meaningful level is a daunting task in the face of the driving force of tolerance. However, rational strategies for overcoming each step in the series of tolerogenic mechanisms have gradually brought immunotherapy into the arena of cancer therapy.

Positive and negative components that, respectively, enhance and suppress immune responses are present in the immune system, as in other physiological systems, and are responsible for maintaining homeostasis. The primordial positive component that triggers virtually any type of immune response is innate immunity. The main reason why the immune system efficiently combats pathogens is that innate immune cells express an abundant array of receptors that recognize various molecules found in microbes. Such recognition provokes intense inflammatory responses and the activation of dendritic cells (DCs), the most potent antigen-presenting cells for T cells. Inflammation and activated DCs subsequently initiate effective antigen-specific immune responses, that is, adaptive immunity. This "innate immunity-DC-adaptive immunity" axis is the essence of the positive immune component.

To prevent immune responses to autologous or innocuous antigens, and to avoid excessive responses to noxious antigens, the immune system has several layers of negative (suppressive) components. First of these is the induction of central tolerance in the thymus, through which high-affinity self-reactive T cells are eliminated. To assure tolerance to innocuous antigens in the periphery, peripheral tolerance is maintained by several mechanisms, among which regulatory T cells play a key role. Furthermore, negative signals transmitted to T cells through inhibitory receptors, such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1), represent crucial molecular mechanisms for the timely termination of T cell responses [1]. In addition, tumor tissues co-opt certain immunosuppressive components, including regulatory T cells, PD-1 ligands, and myeloid-derived suppressor cells, thus creating a microenvironment hostile to tumor-reactive T cells.

These positive and negative components provide targets for provoking antitumor immune responses. In this issue, Dr. Bocchia reviews peptide vaccines derived from antigens that are preferentially expressed by tumor cells, thus

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circumventing self-tolerance at least in part. In addition, developing appropriate adjuvants that are combined with peptide vaccines will be important for improving efficacy by triggering innate immune responses [2]. Dr. Kitawaki reviews DC vaccines that exploit the power of the most potent T cell stimulator. Dr. Fujiwara and Dr. Turtle review adoptive immunotherapy using T cells modified with T-cell receptor or chimeric antigen receptor genes, which bypasses tolerance induced in vivo in cancer patients by transferring tumor-reactive T cells cultured ex vivo. Theoretically, all of these methods can be combined with blockade of the negative immune components to enhance efficacy. In particular, blocking CTLA-4 and/or PD-1 signals, which have been shown to induce remarkable clinical effects by themselves [3], are immediate candidates. The anti-CCR4 monoclonal antibody, which eliminates regulatory T cells, also represents a promising enhancer of antitumor immunity. Such blockade of "immune checkpoints" will constitute an integral component of tumor immunotherapy [1].

Although immunotherapy is generally considered to be "safe", we need to be careful about side effects as efficacy increases. For example, targeting antigens that are expressed by normal cells can cause severe adverse events [4]. Also, blocking inhibitory pathways hardwired into the immune system, which are crucial for maintaining self-tolerance and modulating the amplitude of physiological immune responses, cause collateral tissue damage [1]. We need to take care to minimize these side effects to an acceptable level.

In any event, tumor immunotherapy has certainly begun to come of age. We can expect to observe remarkable advances in the translation of basic findings to clinical applications. In the field of hematological malignancies, immunotherapy will be applied mainly to elderly patients ineligible for allogeneic transplantation. Furthermore, if "autologous" immunotherapy turns out to be truly effective, it may replace part of "allogeneic" immunotherapy as we pursue safer cancer therapies.

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