Conclusions and levels of evidence for nephrotoxicity surveillance in CAYA cancer survivors

Who needs nephrotoxicity surveillance?				
Risk factors for glomerular dysfunction (i.e. decreased GFR, proteinuria), tubular dysfunction and combined glomerular & tubular dysfunction in CAYA cancer survivors diagnosed up to 25 years of age				
	Glomerular dysfunction		**Tubular dysfunction**	**Combined glomerular & tubular dysfunction**
	Decreased GFR	**Proteinuria**		
Treatment factors				
Ifosfamide (y/n)	↑⊕⊕⊕⊕ HIGH	↑⊕⊕⊕⊕ HIGH	↑⊕⊕⊕⊕ HIGH	↑⊕⊕⊖⊖ LOW
Higher ifosfamide dose	↑⊕⊕⊕⊕ HIGH	↑⊕⊕⊕⊕ HIGH	↑⊕⊕⊕⊕ HIGH	↑⊕⊕⊖⊖ LOW
Cisplatin (y/n)	↑⊕⊕⊕⊕ HIGH	=⊕⊖⊖⊖ VERY LOW	↑⊕⊕⊕⊖ MODERATE	=⊕⊕⊖⊖ LOW
Higher cisplatin dose	↑⊕⊕⊕⊕ HIGH	=⊕⊕⊖⊖ LOW	↑⊕⊕⊖⊖ LOW	=⊕⊕⊖⊖ LOW
Carboplatin (y/n)	↑⊕⊕⊕⊖ MODERATE	=⊕⊕⊖⊖ VERY LOW	↑⊕⊖⊖⊖ VERY LOW	No studies
Higher carboplatin dose	↑⊕⊕⊖⊖ LOW	=⊕⊕⊖⊖ LOW	↑⊕⊕⊖⊖ LOW	↑⊕⊖⊖⊖ VERY LOW
MTX (y/n)	=⊕⊕⊕⊕ HIGH	=⊕⊕⊕⊕ HIGH	=⊕⊕⊕⊖ MODERATE	No studies
Higher MTX dose	=⊕⊕⊕⊕ HIGH	=⊕⊕⊕⊖ MODERATE	=⊕⊕⊖⊖ LOW	No studies
MTX administration routes	No studies	No studies	No studies	No studies
Nitrosoureas (y/n)	No studies	No studies	No studies	No studies
Higher nitrosoureas dose	No studies	No studies	No studies	No studies
Melphalan (y/n)	No studies	No studies	No studies	No studies
Higher melphalan dose	No studies	No studies	No studies	No studies

Cyclophosphamide (y/n)	=⊕⊕⊕⊖ MODERATE	=⊕⊕⊕⊖ MODERATE	=⊕⊕⊕⊖ MODERATE	No studies
Higher cyclophosphamide dose	=⊕⊖⊖⊖ VERY LOW	=⊕⊖⊖⊖ VERY LOW	=⊕⊕⊕⊖ MODERATE	No studies
RT kidney area (y/n)	↑⊕⊕⊕⊕ HIGH	↑⊕⊖⊖⊖ VERY LOW	=⊕⊕⊖⊖ LOW	No studies
Higher RT dose	↑⊕⊕⊕⊖ MODERATE	↑⊕⊕⊖⊖ LOW	No studies	No studies
RT one vs. both kidneys	No studies	No studies	No studies	No studies
RT actual portion kidney	↑⊕⊕⊖⊖ LOW*	=⊕⊕⊖⊖ LOW	No studies	No studies
TBI (y/n)	↑⊕⊕⊕⊖ MODERATE	↑⊕⊕⊕⊖ MODERATE	=⊕⊕⊖⊖ LOW	No studies
Nephrectomy (y/n)	↑⊕⊕⊕⊕ HIGH	=⊕⊖⊖⊖ VERY LOW	=⊕⊖⊖⊖ VERY LOW	No studies
Nephrectomy unilateral vs. partial bilateral	No studies	No studies	No studies	No studies
HCT (y/n)	=⊕⊖⊖⊖ VERY LOW	No studies	No studies	No studies
Combination therapy				
Platinum agents + ifosfamide vs. no nephrotoxic therapy	↑⊕⊕⊕⊖ MODERATE	↑⊕⊕⊕⊖ MODERATE	↑⊕⊖⊖⊖ VERY LOW	No studies
RT kidney area + chemotherapy $^{\Delta}$ vs. no nephrotoxic therapy	↑⊕⊕⊖⊖ LOW	=⊕⊕⊕⊖ MODERATE	No studies	No studies
Nephrectomy + RT kidney area vs. no nephrotoxic therapy	↑⊕⊕⊖⊖ LOW	↑⊕⊕⊖⊖ LOW	↑⊕⊖⊖⊖ VERY LOW	No studies
Nephrectomy + chemotherapy $^{\Delta}$ vs. no nephrotoxic therapy	↑⊕⊕⊖⊖ LOW	↑⊕⊕⊖⊖ LOW	No studies	No studies

Nephrectomy + RT kidney areas + chemotherapy $^{\Delta}$ vs. no nephrotoxic therapy	↑⊕⊕⊖⊖ LOW	↑⊕⊕⊖⊖ LOW	No studies	No studies
Combination vs. one modality (additive risk)	No studies	No studies	No studies	No studies
Host factors				
Age ifosfamide exposure	=⊕⊕⊕⊖ MODERATE	No studies	=⊕⊕⊖⊖ LOW	No studies
Older age cisplatin exposure	↑⊕⊖⊖⊖ VERY LOW	No studies	No studies	No studies
Older age carboplatin exposure	↑⊕⊖⊖⊖ VERY LOW	No studies	No studies	=⊕⊖⊖⊖ VERY LOW
Older age cancer treatment	↑⊕⊖⊖⊖ VERY LOW	=⊕⊕⊕⊕ HIGH	↑⊕⊕⊖⊖ LOW	⇳⊕⊖⊖⊖ VERY LOW
Male sex	↑⊕⊖⊖⊖ VERY LOW	=⊕⊕⊕⊖ MODERATE	=⊕⊕⊖⊖ LOW	No studies
Hypertension (y/n)	↑⊕⊕⊕⊖ MODERATE	↑⊕⊕⊕⊖ MODERATE	↑⊕⊕⊖⊖ LOW	No studies
Supportive care drugs				
TBI + aminoglycosides + vancomycin vs. no therapy	↑⊕⊖⊖⊖ VERY LOW	No studies	No studies	No studies
Amphotericin B (y/n)	↑⊕⊖⊖⊖ VERY LOW	↑⊕⊕⊖⊖ LOW	No studies	No studies
Calcineurin inhibitors (y/n)	↑⊕⊖⊖⊖ VERY LOW	No studies	No studies	No studies
Abelcet/ambisome (y/n)	No studies	=⊕⊕⊖⊖ LOW	No studies	No studies
Current use ACEi/ARB	No studies	=⊕⊕⊖⊖ LOW	No studies	No studies
When should surveillance be initiated?				
The course of kidney dysfunction in CAYA cancer survivors diagnosed up to 25 years of age				

Glomerular dysfunction	**Quality of evidence**
Progressive decrease of GFR that parallels the physiological decline of GFR also seen in healthy subjects or CCS without nephrotoxic therapy. However, they have a decreased mean GFR compared to controls (range follow-up 1st – 5th decade)	⊕⊕⊕⊕ HIGH
Tubular dysfunction	
After ifosfamide exposure, the risk of tubular dysfunction increases over time until at least three years following therapy	⊕⊕⊖⊖ LOW

Risk for kidney dysfunction after acute kidney toxicity episode in CAYA cancer survivors diagnosed up to 25 years of age		
Glomerular dysfunction	**Outcome**	**Quality of evidence**
1. eGFR <60 vs. >60 ml/min/1.73m^2 at the time of childhood cancer diagnosis 2. having a history of ≥ 4 AKI episodes vs. no AKI episodes during cancer treatment	Increased risk (decreased GFR)	⊕⊖⊖⊖ VERY LOW
Tubular function	Unknown	No studies

At what frequency should surveillance be performed?

Risk over time of kidney dysfunction in CAYA cancer survivors diagnosed up to 25 years of age

	Glomerular dysfunction		**Tubular dysfunction**		
Treatment	**Outcome**	**Quality of evidence**	**Outcome**	**Quality of evidence**	**Remarks**
Ifosfamide	Unknown	No studies	Improvement hypophosphatemia, hypokalemia, abnormal bicarbonate levels*	⊕⊕⊖⊖ LOW	*The need for supplementation of phosphate and potassium decreases over time and may no longer be needed at 10 years after ifosfamide treatment High ifosfamide dose associated with smaller falls in phosphate and bicarbonate at 10 years compared to 1 year after cancer treatment
Platinum therapy	Unknown	No studies	Stable hypomagnesemia*	⊕⊕⊖⊖ LOW	*Occurs at low levels 1 year after platinum therapy and remains stable up to at least three years
Nephrectomy	GFR decline*	⊕⊕⊕⊖ MODERATE	Unknown	No studies	*Until at least 5th decade since end of treatment

NSS	GFR improvement*	⊕⊕⊕⊖ MODERATE	Unknown	No studies	*At least two decades since end of treatment
Nephrectomy or NSS with pre-operative kidney disease	GFR improvement*	⊕⊕⊕⊖ MODERATE	Unknown	No studies	*Until at least 13 years since end of treatment
HCT	GFR decline*	⊕⊕⊖⊖ LOW	Unknown	No studies	*Early after treatment after which partial improvement and stabilization until at least three years since end of treatment
Other treatment modalities	Unclear*	⊕⊖⊖⊖ VERY LOW	Unknown	No studies	*Studies are incomparable regarding treatment
Predictors for change of risk over time					
	Glomerular dysfunction		**Tubular dysfunction**		**Remarks**
Treatment predictors					
Ifosfamide	=⊕⊕⊕⊖ MODERATE		=⊕⊖⊖⊖ VERY LOW		
Cisplatin	↑⊕⊕⊕⊖ MODERATE*		=⊕⊖⊖⊖ VERY LOW		*More rapid deterioration rate of GFR after higher vs. lower cisplatin dose up to 25 years after diagnosis
Carboplatin	=⊕⊕⊕⊖ MODERATE		=⊕⊖⊖⊖ VERY LOW		
HD-MTX*	=⊕⊕⊕⊕ HIGH		No studies		* > 5g/m^2
HD-cyclo*	↑⊕⊕⊖⊖ LOW**		No studies		* ≥ 1 g/m^2/course or a total cumulative dose of ≥10 g/m^2 ** Modest differences in rate of GFR deterioration after HD- vs. non-HD-cyclophosphamide
Nitrosoureas	No studies		No studies		
Melphalan	No studies		No studies		
RT kidney area	=⊕⊕⊖⊖ LOW		=⊕⊖⊖⊖ VERY LOW		

TBI	↑⊕⊕⊖⊖ LOW*	No studies	* Higher deterioration rate of GFR after TBI vs. no TBI
Nephrectomy	=⊕⊕⊖⊖ LOW	No studies	
HCT	No studies	=⊕⊖⊖⊖ VERY LOW	
Type of HCT	=⊕⊖⊖⊖ VERY LOW	=⊕⊖⊖⊖ VERY LOW	
Host predictors			
Age	See below	No studies	
Nephrectomy age	↑⊕⊕⊖⊖ LOW*	No studies	*Faster decline in GFR after nephrectomy at older vs. younger age
Sex	No studies	No studies	
Other predictors			
AKI*	=⊕⊖⊖⊖ VERY LOW	=⊕⊖⊖⊖ VERY LOW	* < 30 days after HCT
Presence GVHD	=⊕⊖⊖⊖ VERY LOW	=⊕⊖⊖⊖ VERY LOW	
Cyclosporine 1 year after HCT	No studies	=⊕⊖⊖⊖ VERY LOW	
Simultaneous use amphotericin B, vancomycin or gentamycin	=⊕⊖⊖⊖ VERY LOW	No studies	
What surveillance modality should be used?			
Diagnostic value of tests to detect kidney dysfunction in CAYA cancer survivors diagnosed up to 25 years of age			
Variable		**Outcome**	**Quality of evidence**

Methods to detect decreased glomerular filtration rate	eGFR equations based on cystatin C better correlated to measured GFR than eGFR equations based on creatinine in CAYA cancer survivors, although correlation coefficients vary between 0.33 and 0.6	⊕⊕⊖⊖ LOW
Methods to detect glomerular proteinuria	Unknown	No studies
Methods to detect tubular proteinuria	Unknown	No studies
Methods to detect electrolyte disturbances	Unknown	No studies
Diagnostic value of ABPM or HBPM vs. office blood pressure measurement	Unknown	No studies
What should be done when abnormalities are identified?		
Use of medical interventions to improve kidney function in CAYA cancer survivors diagnosed up to 25 years of age		
Variable	**Outcome**	**Quality of evidence**
Effect of electrolyte supplementation	Unknown	No studies
Effect of ACEi or ARB	Unknown	No studies
Effect of antihypertensive agents in general	Unknown	No studies

⬆ indicates an increased risk, = indicates no significant effect, and ⇳ indicates conflicting evidence.

* For ≥5 or ≥10 Gy per % volume of kidney irradiation, no significant effect for ≥15 or ≥20 Gy.

$^{\Delta}$ chemotherapy included: high-dose cyclophosphamide, high-dose methotrexate, cisplatin, carboplatin, and/or ifosfamide.

Abbreviations: ^{99}Tc-DPTA, diethylene-triamine-pentaacetate; ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CKD-EPI, CKD-EPI, chronic kidney disease epidemiology collaboration; creat, creatinine; cys C, cystatin C; (e)GFR, (estimated) glomerular filtration rate; GVHD, graft versus host disease; HBPM, home blood pressure monitoring; HD, high-dose; HCT, hematopoietic cell transplantation; MTX, methotrexate; NSS, nephron sparing surgery; RT, radiotherapy; TBI, total body irradiation; vs, versus; y/n, yes/no.