131I-Meta-iodobenzylguanidine followed by Busulfan and Melphalan and autologous stem cell transplantation in high-risk neuroblastoma

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Abstract

Introduction.Despite progress obtained with current treatments,the event-free survival of high-risk neuroblastoma(HR-NB)patients does not exceed 40-50% and the prognosis in refractory or relapsed patients is poor,still representing a challenge for pediatric oncologist.Therapeutic Iodine-131 meta-iodobenzylguanidine(Th-131I-MIBG) is a recognized safe and potentially effective treatment in NB.Materials.In this retrospective study,we report outcome of 28 MIBG-avid NB patients with advanced disease,because refractory or relapsed,underwent,from 1996 to 2014,to Th-131I-MIBG administered shortly before(median of 17 days) high-dose chemotherapy with Busulfan and Melphalan(HD-BuMel) and autologous stem cell transplantation(ASCT)at Gaslini Institute in Genoa,with the aim to analyze feasibility,safety and efficacy of this approach.Results.Engraftment occurred in all patients after a median of 14(11-29)and 30 days(13-80)from ASCT for neutrophil and platelet respectively.No treatment-related deaths were observed.The main high grade(3-4)toxicity observed was oral and gastrointestinal mucositis in 78.6% and 7.1% of patients respectively,while high grade hepatic toxicity was observed in 10.7%;two patients developed veno-occlusive-disease(7.1%),completely responsive to defibrotide.Hypothyroidism was the main late complication occurred in 9 patients(31.1%).After Th-131MIBG and HD-BuMel, 19 patients(67.8%) showed an improvement of disease status.Over a median follow-up of 15.9 years,the 3-year and 5-year overall survival(OS)probability were 53%(CI 0.33-0.69)and 41%(CI 0.22-0.59)and the 3-year and 5-year rates of cumulative risk of progression/relapse were 64%(CI 0.47-0.81)and 73%(CI 0.55-0.88),respectively.MYCN amplification emerged as the only risk factor significantly associated with OS(HR 3.58;p0.041).Conclusion.Th-131I-MIBG administered shortly before HD-BuMel turned out to be a safe and effective regimen,suggesting it should be included in a sequential approach in patients with advanced MIBG-avid NB.These patients could be benefit to be manage in centers with proven expertise in these treatments.

INTRODUCTION

Neuroblastoma (NB) is the most common extra-cranial solid tumor in childhood **[1]** . Its prognosis depends on the stage, age and molecular features on diagnosis.

In cases of high-risk (HR) NB, the chances of cure remain poor, with 3- and 5-year event-free survival rates of 40-50% **[2-5]** . The current treatment of HR-NB consists of multimodal approaches that include surgical resection of the primary tumor, induction chemotherapy, high-dose myeloablative therapy (HD-MAT) followed by autologous stem cell transplantation (ASCT), radiotherapy, retinoic acid and immunotherapy with chimeric anti-GD2 antibody.

Scintigraphy with ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) is recognized to be an effective and reliable method of staging and evaluating the response to treatment of NB patients **[6]** , while meta-

iodobenzylguanidine radiolabeled with iodine-131 (^{131}I-MIBG) has been successfully used as a targeted treatment, administered alone in relapsed/refractory HR-NB or combined with chemotherapy and ASCT[**17-24**] . This treatment exploits the avidity of NB cells in taking meta-iodobenzylguanidine into the cytoplasm and mitochondria through norepinephrine transporter channels, potentially delivering a lethal radiation dose to the target cells [**7-9**] .

The main aim of this retrospective study was to analyze the feasibility and toxicity of therapeutic^{131}I-MIBG (Th-^{131}I-MIBG) followed closely by ASCT conditioned with HD-MAT with Busulfan and Melphalan (BuMel) in children affected by HR-NB with residual MIBG-avid disease.

The secondary aim of the study was to evaluate the cumulative risk of progression/relapse (CRR) and the overall survival (OS) and to analyze the association of the principal risk factors with outcome.

MATERIALS AND METHODS

We retrospectively analyzed patients with refractory or relapsed NB treated at the GianninaGaslini Institute in Genoa (Italy) from 1996 to 2014. Those who had undergone treatment with Th-^{131}I-MIBG followed closely by ASCT after HD-MAT with Busulfan and Melphalan after induction therapy were included in the analysis, while those who had received Th-^{131}I-MIBG alone or in combination with a different schedule of HD-MAT were excluded.

Figure 1 summarizes treatment schedules and disease response evaluations.

All patients or their guardians signed a consent form allowing the use of their data for clinical research purposes. We followed the procedures in accordance with our institution's ethical standards and according to Italian guidelines. The Liguria Regional Ethics committee (ComitatoEticoRegionale – Regione Liguria – IRCCS AOU San Martino – IST) approved the collection for retrospective studies (360REG2014) of data from medical records of patients admitted to our department.

All data were collected from our institutional database and retrospectively analyzed. The main clinical characteristics of patients and the types of treatment are summarized in **Table 1** .

Criteria for diagnosis, staging and inclusion in the study

The diagnosis of NB was established by histological examination of tumor specimens or by bone marrow infiltration and/or elevated urinary excretion of catecholamine metabolites. Disease extension on diagnosis and response to treatment were evaluated by means of imaging (ultrasonography/CT scan/MRI) of the primary tumor,^{123}I-MIBG scintigraphy and study of bone marrow on at least 2 aspirates and 2 trephine core biopsies. In the absence of MIBG uptake, skeletal involvement was evaluated by means of technetium 99m-MDP scintigraphy or, more recently, ^{18}F-FDG PET/CT. However, in this specific case, the patient was not deemed eligible for the study. All patients were staged according to INSS criteria [**10**] . MYCN gene amplification was defined as a copy number of 10 or more.

To be included in the study, patients had to have a poorly responding HR-NB (MIBG-avid) after induction followed by further chemotherapy or, alternatively, a residual HR-NB (MIBG-avid) after a salvage treatment for relapse.

Treatments: Induction therapy, PBSC harvest and Th-^{131}I-MIBG

Induction therapy was administered according to the Italian NB97 protocol [**14**] before 2002 and the European SIOPEN NBAR-01 protocol [**15**] in subsequent years. Patients with refractory disease after induction underwent salvage therapy with additional courses of chemotherapy (*ICE* and/or *TVD and/or TEMIRI*).

Peripheral blood stem cells (PBSC) were collected only if bone marrow evaluation (at least 2 aspirates and 2 biopsies from different sites) demonstrated complete remission; collection was performed after stimulation with Granulocyte Colony-Stimulating Factor (G-CSF), administered subcutaneously at a dosage of 10 μg/kg/day. The minimum CD34+ cell-dose required in order to consider collection to be adequate was 3 x 10^6/kg of the recipient's weight (optimal dose [?] 4 x 10^6/kg).

Before ^{131}I-MIBG administration, patients underwent thyroid blockade according to EANM procedure guidelines[**16**] and showed normal organ function and a value of WBC > 2000/uL and of platelets > 75000/uL. They were then admitted to the Nuclear Medicine Department, where Th^{131}I-MIBG was administered in a single intravenous infusion over 2 hours (median dose 8.5mCi/Kg [IQR 6.5-12]). All patients remained in radiation protective isolation for 5-7 days after^{131}I-MIBG administration.

High-dose BU-Mel and autologous stem cell transplantation

High-dose chemotherapy consisted of Busulfan, administered in 16 doses from day -7 to day -3 before ASCT; administration was oral until 2011 (cumulative dose 16 mg/kg) and intravenous in the following years (cumulative dose according to weight range: *<9 Kg: 16 mg/Kg; 9-16 Kg: 19.2 mg/Kg; 16-23 Kg: 17.6 mg/Kg; 23-34 Kg: 15.2 mg/Kg; >34 Kg: 12.8 mg/Kg*). Melphalan was administered on day -1 in a single intravenous dose of 140 mg/m^2. On day 0, patients underwent ASCT.

Disease response criteria and toxicity

Disease response was evaluated at the end of the induction phase, before and after Th-^{131}I-MIBG and HD-BuMel, at the end of treatment and at the last follow-up examination.

Considering the disease response evaluated before Th-^{131}I-MIBG and HD-MAT BuMel, according to the International Neuroblastoma Response Criteria (INRC) [**10**] , we defined 3 groups of response: i) *good response* (complete response [CR], very good partial response [VGPR]); ii)*partial response* (PR); iii) *poor response* (no response [NR], stable disease [SD] and progression of disease [PD]).

Toxicity was graded according to Common Terminology Criteria version 4.03 [**11**] , on considering mucosal, gastrointestinal, pulmonary, hepatic and renal toxicities and veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) according to the Baltimore [**12**] and Seattle criteria [**13**] . Only proven bacterial bloodstream infection or clinical sepsis and deep mycosis were regarded as significant infective complications. Engraftment was defined as the first of 3 consecutive days on which neutrophil and platelet counts reached 500/mm^3 and 50,000/mm^3, respectively.

Statistical analysis

Descriptive statistics are reported in terms of absolute frequencies and percentages for continuous data), and Pearson's chi-square test was used to compare proportions.

The overall survival (OS) probability and the cumulative risk of relapse (CRR) were calculated by means of the Kaplan-Meier method, considering time from diagnosis and from therapy (Th-^{131}I-MIBG and HD-MAT BuMel) to death from any cause (for OS) or to relapse (for CRR); if neither event occurred, data were censored on the date of the last follow-up examination. Differences among subgroups were assessed by means of the Log Rank test. Cox modeling was adopted for multivariate analysis, considering MYCN amplification, induction therapy, MIBG score after induction, HD-CT with Thiotepa and disease status before Th-^{131}I-MIBG as variables.

Analyses were performed by means of STATA software (version 14.2, Stata Corp., College Station, TX, USA). Two-tailed probabilities are reported; a p-value of 0.05 was adopted to define nominal statistical significance.

RESULTS

From 1996 to 2014, 198 patients with high-risk NB underwent HD CT followed by ASCT at a median age of 4.16 years (0.35 – 23.67) at GianninaGaslini Institute in Genoa (Italy); 28 (14.1 %) of these were treated, after induction or salvage therapy and further chemotherapy, with additional Th-^{131}I-MIBG closely followed by HD-MAT BuMel and ASCT as part of consolidation treatment, and were therefore deemed eligible for this retrospective study. Twenty-four patients (85.7 %) were newly diagnosed (all but one stage 4) with refractory disease after induction therapy, and 4 (14.3%) were enrolled after relapse (2 stage 4, 1 stage 4s and 1 stage 2), which occurred after a median time from diagnosis of 68 months (range 27 – 84).

At the end of induction therapy, all 28 patients showed residual MIBG-avid disease: 12 showed partial response (42.86 %) and 16 poor response (57.14 %) (**Table 1**); 7 patients (25%) received an additional course of HD-MAT with Thiotepa followed by ASCT.

High-dose BU-Mel and autologous stem cell transplantation and acute toxicities

The conditioning regimen with Busulfan and Melphalan was started a median of 17 days (IQR 14 – 25) after Th-^{131}I-MIBG; the median dose of autologous CD34+ cells grafted was 4.6 x 10^6/kg (2.9 – 10).

In all patients, neutrophil and platelet engraftment occurred a median of 14 days (11 – 29) and 30 days (13 – 80), respectively, after ASCT. Oral mucositis was the main toxicity observed after Th-^{131}I-MIBG and HD-BuMel, occurring in all patients (28, 100%): high-grade (3 - 4) in 22 (78.6%) and low-grade (1 - 2) in 6 (21.4%). Gastrointestinal involvement occurred in 6 patients (21.4%): grade 4 in 2 (7.1%) and grade [?] 2 in 4 (14.3%). No pulmonary toxicity was observed, while renal involvement was observed in 1 (grade 2). Hepatic toxicity was observed in 20 patients (71.4%): grade 1 - 2 in 17 (60.7 %) and grade 3 – 4 in 3 (10.7 %). Two patients developed VOD/SOS(7.1%), which resolved completely after treatment with defibrotide. Only one patient developed sepsis (Gram-) and no deep mycosis was observed.

Treatment after Th-^{131}MIBG and HD BU-Mel

All patients completed the therapeutic protocol with 6 courses of oral isotretinoin. Eleven patients (39.3%) received immunotherapy with anti-GD2 antibody.

Disease response, relapse, survival and late toxicities

After Th-^{131}I-MIBG and HD-MAT BuMel, 10 patients (35.7%) obtained a good response (CR, VGPR), 11 (39.3%) and 7 (25%) obtained partial and poor responses, respectively. In summary, 19 (67.8%, p <0.05) patients improved their disease status after Th-^{131}MIBG and HD BU-Mel (**Table 2**).

Twenty patients suffered relapse after the end of treatments (71.4%) at a median time of 3.2 years (0.2 – 13.2) after ASCT (17 out of 24 newly diagnosed, 3 out of 4 relapsed) in metastatic sites in 13 (46.4%), in primary site in 3 (10.7%) and combined (primary + metastatic) in 4 (14.3%).

Hypothyroidism requiring hormone replacement therapy occurred after a median of 11.5 months after ASCT (5.1 – 16.8) in 9 patients (31.1 %), without significant differences of induction therapy, median dose of Th^{131}-I-MIBG, thyroid blockade treatment or age on ASCT from patients who did not develop thyroid failure; two patients developed benign thyroid nodules, while no secondary malignancies were diagnosed.

Over a median follow-up of 15.9 years (IQR $1^{st}q$ 7.0 – 3^{rd} q 16.9) after Th-^{131}I-MIBG and HD-MAT BuMel, 15 patients (53.6%) died of disease progression. Of the 13 (46.4%) surviving patients, 4 (14.3%) were disease-free and 9 (32.1%) had stable residual disease**(Table 3)** . No toxic deaths occurred.

The 3-year and 5-year rates of overall survival (OS) probability were 53% (CI 0.33 – 0.69) and 41% (CI 0.22 – 0.59) respectively**(Figure 2)** and the 3-year and 5-year rates of cumulative risk of relapse were 64% (CI 0.47 - 0.81) and 73% (CI 0.55 – 0.88), respectively **(Figure 3)** . In terms of OS and CRR, no differences were observed between the entire cohort and the 24 newly diagnosed patients (3-year and 5-year OS probability 54% [CI 0.32 – 0.71] and 39% [CI 0.20 – 0.58], respectively; 3-year and 5-year CRR 67% [CI 0.48 – 0.84] and 72% [CI 0.53 – 0.88], respectively).

On Cox multivariate analysis, MYCN amplification emerged as the only risk factor significantly associated with OS (HR 3.58; p 0.041), while the other variables considered were not significantly associated with outcome. In particular,^{123}I-MIBG score (< 3 *versus* [?] 3) and disease response before Th-^{131}I-MIBG were not associated with outcome **(Table 4)** .

DISCUSSION

The results of this study suggest that Th-^{131}I-MIBG administered shortly before HD CT BuMel and ASCT is a feasible, safe and effective regimen in patients with advanced NB. To our knowledge, this cohort is the

largest described in the literature on HR-NB patients treated with this combination.

Treatment of high-risk NB is currently a challenge for pediatric oncologists. Indeed, despite the improvement obtained with recent protocols, event-free survival (EFS) remains unsatisfactory. Data from the Italian registry **[3]** on the outcome of NB patients over the years showed a steady improvement in OS in patients with lower stages of disease; in stage 4 patients, by contrast, after a significant increase from the 1980s to the 1990s (from 6.7% to 20.6%), OS remained stable in the early 2000s (29.3 %). More recently, data from the randomized HR-NBL1/SIOPEN trial showed a 3-year rate of EFS in HR-NB (stage 4) ranging from 33 to 49% according to the HD CT regimen (CEM vs BuMel), and indicated that BuMel was the better of the two conditioning regimens in stage 4 **[2]** . Moreover, the 5-year overall survival rate of HR-NB patients in the Children's Oncology Group between 2005 and 2010 was 50% **[17]** . These poor outcomes mean that it is mandatory to explore new therapeutic approaches, since the benefit of intensified chemotherapy seems to be approaching the end of its potential.

Th-^{131}I-MIBG has proved to be an effective and reliable targeted therapy in relapsed or newly diagnosed NB, with an overall response rate of about 30% in several studies**[17-24]** , the majority of which have concerned small series of patients treated with various schedules of Th-^{131}I-MIBG, either alone or combined with various myeloablative chemotherapies. The rationale of Th-^{131}I-MIBG lies in the propensity of NB cells to internalize ^{131}I-MIBG within the cytoplasm and mitochondria through norepinephrine transporter channels, thereby delivering a lethal radiation dose to the tumor while limiting the damage to healthy tissues **[23, 24]** . Moreover, its activity seems to be increased by combination with other agents.

Previous studies have focused on the safety of combining Th-^{131}I-MIBG and myeloablative treatments. Gaze et al.**[25]** reported the feasibility and good tolerability of Th-^{131}I-MIBG combined with melphalan and total-body irradiation in 5 children with advanced NB. In larger numbers of patients, other groups **[7, 26]** found that the addition of Th-^{131}I-MIBG to a CEM regimen did not affect the toxicity profile of CEM or bone marrow reconstitution after ASCT. Moreover, Lee et al. reported the results of incorporating 131I-MIBG treatment into tandem therapy with ASCT and chemotherapy in which CEC (carboplatin + etoposide + cyclophosphamide) and TM (thiotepa + melphalan) were used as the first and second HDCT regimens, respectively) **[27]** .

The combination of Th-^{131}I-MIBG with HD CT BuMel has previously been reported by French et al. **[28]** . In 8 children with refractory NB who received HD BuMel 6-8 weeks after Th-^{131}I-MIBG, no significant impact on treatment-related toxicity was seen and 5 of 7 evaluable patients with refractory disease achieved either a complete or partial response. More recently, in a case series of 9 patients,Ferry et al. **[29]**confirmed the safety of Th-^{131}I-MIBG (up to 24 mCi/kg) and topotecan combined with HD CT BuMel, administered 2 months later.

In our study, a cohort of 28 children with advanced HR-NB, either newly diagnosed or relapsed, received Th-^{131}I-MIBG (median dose 8.5mCi/Kg) shortly (median 17 days) before HD CT BuMel because of poor response to treatment. This combination proved feasible and well-tolerated, since the toxicities observed were no greater than would be expected after HD BuMel**[2]** and no toxic death occurred. Th-^{131}I-MIBG did not seem to influence the time to engraftment or organ toxicities.

VOD/SOS was diagnosed in only 2 patients (7.1 %), who did not present any significantly different features. This incidence is considerably lower than that reported after Busulphan in the HR-NBL1/SIOPEN trial (18%) **[2]** but similar to that seen among NB patients in the Italian Pediatric Hemato-Oncology Association Group study on the incidence of VOD/SOS **[30]** .

Hypothyroidism was observed in more than one third of patients and can therefore be regarded as a high-incidence late complication after these treatments. This could be due to an increased risk of thyroid failure following high-dose chemotherapy with busulphan and melphalan in patients previously treated with Th-^{131}I-MIBG, despite the administration of thyroid-blocking treatment before this latter.

That adding Th-^{131}I-MIBG before HD CT can improve disease response or survival in HR-NB patients has

already been hypothesized in previous studies [**7-9, 21, 28, 29**] . However, the retrospective nature of our study, which did not include a control group of patients with the same features who did not receive Th-^{131}I-MIBG, prevents us from drawing any definitive conclusions regarding the effectiveness of this approach. Nevertheless, considering the dismal prognosis of the patients included, the overall disease response (67.8%) and the OS probability observed (53% and 41% at 3 and 5 years, respectively), we may suggest that the combination of Th-^{131}I-MIBG given 2-3 weeks before HD BuMel and ASCT is a potentially valid approach in advanced NB patients with MIBG-avid disease.

Despite these encouraging results, our study has some limitations, such as its retrospective, single-center nature, which may have introduced a selection bias, thereby reducing the reliability of our data. Nevertheless, the main strength of this study lies in the number of patients treated by means of the same approach; this aspect is particularly valuable in a subgroup of patients with a very poor prognosis who require the collaboration of a multidisciplinary team, in that it yields useful information on the clinical effect of this treatment.

Another limitation concerns the relatively low median activity of^{131}I-MIBG administered in these patients, in comparison with more recent therapeutic approaches [**31,32**] ; this may have reduced its potential antitumor effect. However, the doses of 131I-MIBG in our patients were in line with, or slightly higher than, those that had proved effective in previous studies in which 131I-MIBG was not combined with chemotherapy) [33].

Recent data on the positive role of immunotherapy with antibody anti-GD2 in improving survival in HR-NB [**31, 32**] could suggest that Th-^{131}I-MIBG administration shortly before HD BuMel should be included in a sequential approach with immunotherapy in HR-NB patients with MIBG-avid disease. For this purpose, it would be advisable to centralize poorly responsive patients with MIBG-avid disease in centers with proven expertise in the administration of Th-^{131}I-MIBG and in the management of HD CT and ASCT. Moreover, these centers should share protocols for treatment, thyroid blockade, patient surveillance and the monitoring of residual radioactivity.

Randomized prospective studies are needed in order to confirm the feasibility and the impact of the above-described strategy on the long-term outcome of HR-NB patients and to define both the^{131}I-MIBG activity with the highest efficacy/toxicity ratio and the best timing for combination with high-dose chemotherapy. The next SIOPEN phase II protocol VERITAS (*ClinicalTrials.gov Identifier: NCT03165292*), which will compare topotecan plus Th-^{131}I-MIBG *versus* HD CT with Thiotepa before HD CT BuMel in very HR NB patients, may provide useful information on these issues.

CONFLICT OF INTEREST STATEMENT

The authors declare to not have any conflict of interest.

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Figure 1. Treatment schedule and disease response evaluation

Figure 2. Overall survival probability

Figure 3. Cumulative risk of relapse

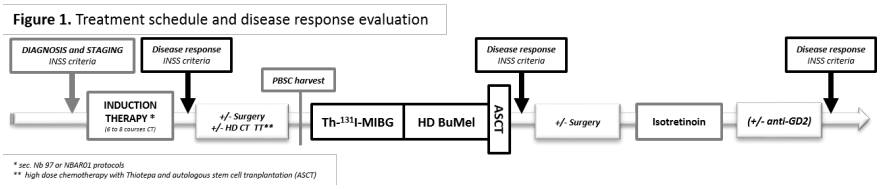


Figure 2. Overall survival probability

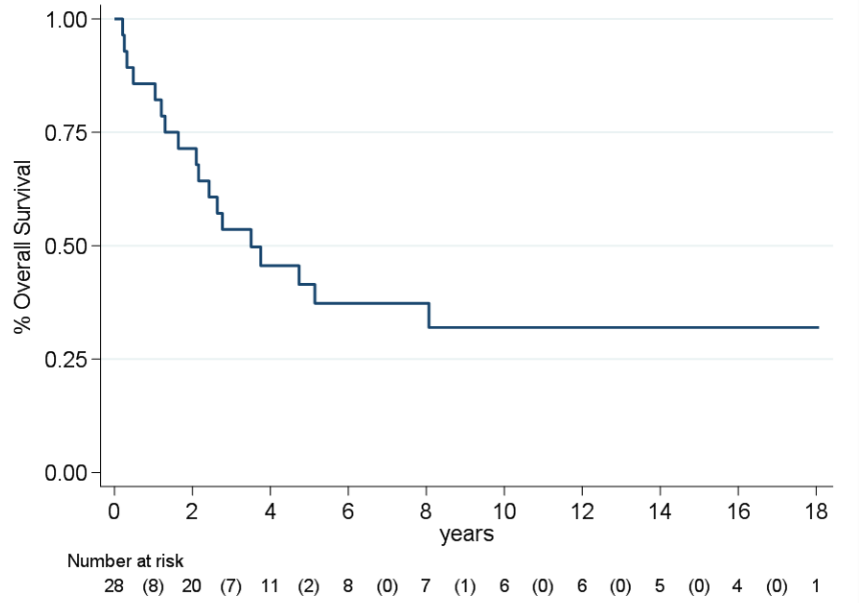
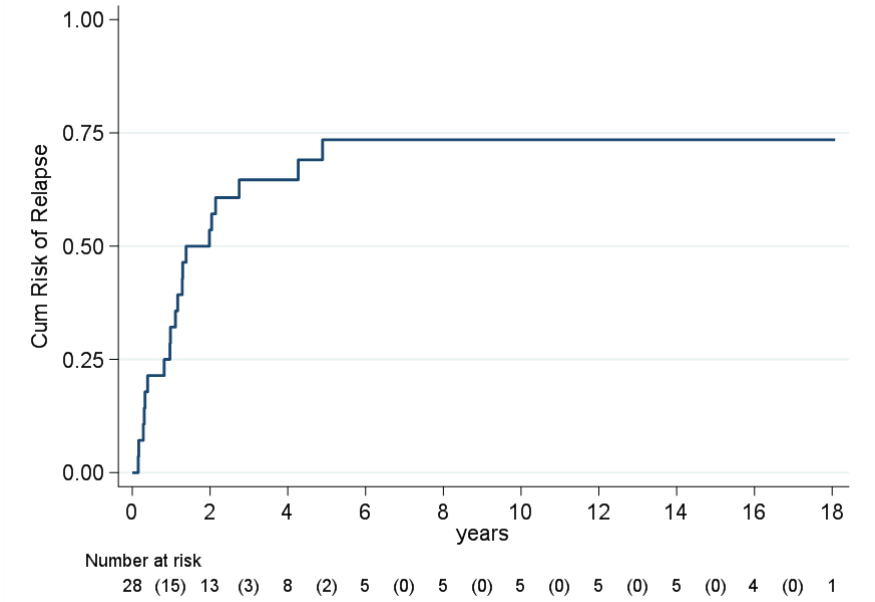


Figure 3. Cumulative risk of relapse



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